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Female	114.7	116.4	117.7	118.7	120.4	123.6	127.1	129.8	132.5	133.7	135.4
DIASTOLIC **Male	76.4	78.1	78.8	79.5	80.4	81.4	82.3	83.3	84.3	84.5	84.0
Female	75.8	77.1	78.0	78.6	79.9	81.9	83.9	85.4	86.8	86.8	84.4

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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

AUGUST, 1952

ORIGINAL ARTICLES

BONE MARROW AND CARCINOMA OF THE PROSTATE†

By James A. Clifton, M.D.
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Recent years have shown a revival of interest in the feasibility of diagnosing metastatic carcinoma by bone marrow aspiration. A great deal of work was published in this field, particularly in Europe, following the report by Rohr and Hegglin in 1936[5]; and, in this country several papers have appeared within the past 5 years, notably those by Rundles and his co-workers. In a review of these papers we were impressed by the wide variance in the incidence of positive results. From a compilation of publications appearing before 1945 we find 100 positive sternal aspirations out of 621 patients so examined[4]. This is an incidence of 16%. Included were malignancies of all types, with and without other evidence of metastases. In 1949 Rundles and Jonsson[6] reported 30 cases of malignant disease of the prostate in which bone marrow aspirations were done. Of these, 56% had cancer cells in the marrow. Puncture sites were not limited to the sternum, and, indeed the needle was inserted into areas shown by roentgenograms to be abnormal or into places with bone pain or tenderness. However carcinomatous cells were found in the sternum in 15 of these cases, an incidence of 50%, and in 2 additional cases carcinoma cells were found in aspirations from the iliac crest. The same authors[7], reporting on 152 patients with all types of carcinoma, recently, found 41% with positive

† Aided in part by grant from the Iowa Cancer Society for Cancer Research.

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TABLE 1.—CLINICAL DATA AND BONE MARROW FINDINGS IN 57 CASES OF CARCINOMA OF THE PROSTATE

No.	Age	Roentgenogram	Bone Marrow	Hemoglobin (gm.)	WBC	Differential Count												Malignancy*	Acid Phosphatase†	Alkaline Phosphatase†	Blood Urea N	Creatinine	Bone Pain
						Neutrophil	Band	Metamyelocyte	Myelocyte	Promyelocyte	Myeloblast	Eosinophil	Basophil	Lymphocyte	Monocyte	Normoblast	Plasmocyte						
1.	77	−	+	14	9700	60.5	7.5		1.5			1.5	2.0	23.0	3.5	0.5		2+	2.6	32.2	16	1.6	−
2.	70	−	−	11	7650	67.5	5.0					3.5	0.5	19.5	4.0			3+	0.2	4.8	18	1.2	−
3.	57	−	+	9	12500	44.0	15.5	4.0	9.0	0.5				21.5	1.5	4.0		2+	...	...	12	1.0	+
4.	75	−	−	13	6400	65.5	18.0	0.5					0.5	11.5	3.5			2+	0.0	2.6	18	1.4	−
5.	70	+	+	8	7250	55.5	12.0					1.0	0.5	23.0	8.0			4+	23.6	20.0	18	1.4	+
6.	80	+	−	12	6000	54.0	2.0					5.5	1.0	33.5	4.0			...	...	...	18	1.0	+
7.	71	−	−	10.9	16750	63.0	14.0					3.0		13.0	6.0		1.0	2+	0.31	2.86	16	1.6	−
8.	72	+	−	11.5	8100	82.0	4.0							8.0	6.0			3+	4.4	8.6	22	1.4	+
9.	70	−	−	13	10400	61.5	1.0					3.0	1.5	24.0	9.0			3+	1.89	2.57	15	1.0	−
10.	70	−	−	11.5	8250	60.5	20.5					0.5	0.5	11.0	7.0			2+	0.8	4.4	15	1.6	−
11.	76	+	−	8	9800	59.0	2.5		1.0			1.0		29.5	6.0	1.0		3+	0.72	6.45	29	1.8	−
12.	81	−	−	12.5	15300	66.5	5.5					3.5		18.0	6.5			3+	0.1	2.46	15	1.4	−
13.	87	−	−	13	16500	70.5	7.0		0.5			0.5		16.5	5.0			3+	...	...	16	1.2	+
14.	73	+	−	12	6200	48.0	5.0		0.5			5.5	1.0	30.5	9.5			...	0.0	4.0	22	1.2	−
15.	59	+	+	13.5	11200	45.5	6.5					2.5	1.0	37.5	7.0			3+	1.6	4.0	13	1.0	+
16.	84	−	+	13	12000	46.0	8.5	0.5	2.5			0.5	0.5	32.5	9.0			4+	...	...	23	1.4	−
17.	74	−	−	...	...	58.5	8.0					1.5		25.0	7.0			1+	...	...	...	...	−
18.	74	−	−	13	10500	70.5	10.0					1.0	0.5	16.0	2.0			3+	0.8	1.6	21	1.4	−
19.	85	−	−	13	12600	56.0	6.0					1.0	0.5	26.0	10.5			3+	0.48	2.88	18	1.0	−
20.	79	−	+	13	6100	60.0	22.5		0.5			3.0		9.5	4.5			2+	2.5	8.4	18	1.6	−
21.	55	+	+	11.5	4850	44.5	1.0					4.0	0.5	44.5	5.5			...	4.4	5.6	16	1.4	+
22.	75	−	−	13.5	7900	70.5	1.5					1.5	1.0	20.5	5.0			2+	1.2	4.8	20	1.2	−
23.	79	+	+	14.5	11800	59.5	14.5		3.5	0.5		1.0	2.0	14.0	5.0			4+	2.0	2.0	19	1.0	−
24.	72	−	−	15	12400	45.0	11.0					1.5	0.5	36.5	5.5			3+	1.36	2.18	22	2.0	−
25.	79	−	−	11.3	5700	48.0	4.0		0.5			3.0	0.5	42.5	1.5			2+	0.21	2.44	15	1.2	−
26.	75	+	+	15	9300	56.0	5.0					2.5		30.0	6.5			...	0.8	7.6	22	1.0	+
27.	73	+	+	10.5	13000	46.5	2.0	1.0				24.0	0.5	19.5	6.5			2+	8.8	4.0	15	1.0	+

27.	73	+	+	10.5	13000	46.5	2.0	1.0				24.0	0.5	19.5	6.5			2+	8.8	4.0	15	1.0	+
28.	75	+	+	9.1	14200	74.5	6.0		1.5			0.5	0.5	12.0	5.0			3+	66.94	37.79	18	1.4	+
29.	74	+	+	6.5	3700	46.0	5.0		1.5				0.5	39.0	4.0	4.0		2+	0.4	6.8	29	1.6	+
30.	76	+	−	11.5	6800	62.5	9.5					2.0	1.0	18.0	7.0			2+	0.4	7.6	14	1.4	−
31.	80	−	+	8.7	13300	31.5	2.5		0.5			37.0	2.0	24.5	2.0			3+	1.87	8.07	16	1.2	−
32.	78	−	−	14.5	10400	50.5	5.0					9.0	1.0	27.5	7.0			2+	0.86	1.83	18	1.6	−
33.	74	+	−	12	6500	49.0	3.0					6.0	0.5	34.5	7.0			3+	0.28	1.68	19	1.0	−
34.	65	−	−	14	8000	34.5	3.0					2.0	0.5	54.5	5.0		0.5	2+	0.7	2.8	22	2.0	−
35.	87	+	−	14.5	8500	73.0	6.0	1.0	0.5	0.5		0.5		15.0	3.5			2+	66.8	52.4	25	2.0	−
36.	78	+	+	8	6700	...	...	...	...	...	...	...	...	...	...	...	...	...	26.1	44.5	27	1.6	+
37.	57	+	+	10.5	8800	16.0	15.5	9.5	11.5	0.5	1.5	2.0	1.5	21.0	9.5	11.5		...	76.0	6.8	...	...	+
38.	73	−	−	12	19800	78.5	7.0						2.0	8.0	4.5			4+	...	...	74	3.2	−
39.	70	−	−	13	7500	59.5	9.0					3.0	0.5	27.0	1.0			2+	0.42	2.76	26	1.2	−
40.	64	+	+	10	15700	...	...	...	...	...	...	...	...	...	...	...	...	...	3.0	...	10	1.2	+
41.	61		−	12	11650	54.0	0.5	0.5				2.5		38.5	4.0			3+	0.3	2.2	54	4.0	−
42.	68	−	−	10	7500	71.0	1.0							23.5	4.5			4+	...	...	26	1.2	−
43.	73	+	−	13	11000	49.5	0.5					1.0		48.0	1.0			3+	...	...	20	1.6	+
44.	67	−	−	13	10600	54.5	3.5					2.0		35.0	5.0			3+	1.0	15.0	24	1.8	−
45.	85	−	−	11	10280	58.0	2.5					2.5		30.0	7.0			2+	0.4	2.1	28	2.2	−
46.	81	+	+	7.5	5200	37.5	6.0		0.5			1.0		38.5	5.0	11.5		4+	0.7	9.1	29	1.4	−
47.	64	−	−	12.5	9600	46.5	2.0					3.0	3.0	42.5	3.0			1+	0.55	2.65	24	1.6	−
48.	70	−	−	12	7650	41.5	3.5					1.0	0.5	47.5	6.0			4+	0.45	2.2	20	1.0	−
49.	70	+	−	12	8600	65.5	2.5	0.5	0.5			5.5		20.5	5.0			...	0.2	5.3	15	1.4	+
50.	70	−	−	10	9500	75.0	4.5							15.5	5.0			...	0.4	1.8	24	2.0	−
51.	78	−	−	13	5900	64.0	2.0					1.5	0.5	25.5	6.5			2+	0.1	1.0	27	1.4	−
52.	65	+	+	11	9600	67.0	1.5					1.0	0.5	26.5	3.5			3+	0.1	2.4	15	1.2	+
53.	67	−	−	14.5	13350	74.5	4.0					0.5	0.5	10.5	10.0			3+	0.2	1.8	19	1.2	−
54.	69	−	−	14	5700	76.0	8.0					0.5		5.0	10.5			...	0.2	1.0	27	1.8	−
55.	73	−	−	...	8750	62.0	1.5					1.5		28.5	6.5			...	0.2	2.0	21	1.6	−
56.	70	−	−	12	26450	59.0	5.5					3.5		29.0	3.0			3+	0.3	1.6	16	1.4	−
57.	74	+	+	12	7750	60.5	7.5		0.5			2.5		23.5	5.5			...	17.0	22.0	17	1.2	+

* Plus numbers refer to malignancy grade according to Broder's classification.
† Expressed as Bodansky units. Normal: acid 0.0–1.5; alkaline 1.5–4.0.

bone marrows. The sternal marrow was positive in 50 of these cases.

It occurred to us that perhaps we could reconcile some of these differences by another approach. Actually, what we are endeavoring to determine is whether or not, in a given patient with malignant disease, the bone marrow aspirations are of sufficient value to change the method of treatment or the prognosis. In a patient with known carcinoma the presence or absence of carcinoma cells in material aspirated from an osteolytic or osteoblastic lesion of the skeleton is not going to alter either of these factors. However, in a patient with known carcinoma and without any other evidence of metastases, the demonstration of metastatic cells in the marrow would be of prime importance. Obviously, the failure to demonstrate these cells would not necessarily mean they were absent. Thus, the problem becomes relatively simple: in what percentage of patients with carcinoma can metastatic cells be detected in bone marrow with simple techniques available to the practicing physician who has adequate knowledge of bone marrow morphology? Is bone marrow examination within the range of practicality as regards time, effort, expense, and convenience both to the physician and to the patient?

To begin the study we chose carcinoma of the prostate because of its tendency to metastasize to bone and, especially, to bones of the pelvis. We wanted to compare the frequency of positive results from sternal and iliac punctures. We had a large group of pathologically proved cases of prostatic carcinoma and this afforded the opportunity to study correlations between the degree of anaplasia of the primary tumor and bone marrow spread. Also we correlated various other determinations, such as phosphatase activity, peripheral blood picture, and bone pain with the bone marrow findings.

Subjects and Methods. A total of 57 patients were studied in this report. The diagnosis of carcinoma of the prostate was substantiated by histological examination in 49 cases. In 8 cases, the diagnosis was made by several urologists on the basis of physical examination and roentgenographic findings. The patients were referred from the Department of Urology and were unselected consecutive admissions with the diagnosis of prostatic carcinoma. The presence or absence of roentgenographic changes of bones was not known at the time of the bone marrow puncture. Routinely, we aspirated bone marrow from the manubrium of the sternum[5], and the right iliac crest. Rarely, the left iliac crest was used, the choice being dictated by convenience. The iliac aspirations were done from the upper iliac crest with the patient in the lateral recumbent position. A site on the external surface of the ilium immediately below the crest and anterior to the tensor fascia lata was entered, the needle being directed cephalad to enter beneath the lip. Eight direct marrow smears were made from each puncture site, thus giving a total of 16 slides from each patient. These were stained with buffered Wright's and scanned under the low power objective. Detailed identification was then done, utilizing the oil immersion lens. Peripheral blood smears were made at the time of the marrow puncture and routine 200 cell differential counts were performed.

Roentgenograms of the pelvis and lumbar spine were made on 56 patients and, in addition, the majority had films of the chest and other areas.

Results. Table 1 presents the detailed data on all 57 patients. Explanatory footnotes are included.

Only 18 patients (32%) complained of pain; 17 of these had positive roentgenograms or positive bone marrow smears or both. Eleven patients with bony spread of their disease were without pain. In those with metastases, pressure over the involved bones frequently produced pain.

Positive bone marrow aspirations totaled 19 cases (33%). Twenty-three cases (40%) had roentgenographic evidence of metastases; in 14 of these, carcinoma cells were found in the bone

marrow. Of major significance was the finding of carcinoma cells in the bone marrow aspirations in 5 cases in which there was no roentgenographic evidence of bone involvement. Thus, by use of routine bone marrow puncture, 8.7% of the patients in this series were found to have metastatic carcinoma that otherwise would not have been detected at the time of the examination. The implications of this finding are evident. By utilizing both of these diagnostic aids a total of 28 patients (49%) were found to have bone marrow metastases.

TABLE 2.—INCIDENCE OF POSITIVE MARROW ASPIRATIONS IN 57 CASES OF CARCINOMA OF THE PROSTATE

	No. of Cases
Positive sternum; positive ilium	10
Positive sternum; negative ilium	1
Positive sternum; no iliac specimen	5
Positive ilium; negative sternum	1
Positive ilium; no sternal specimen	2

Table 2 details the number of positive aspirations from each site. In the total of 19 positive bone marrows the sternum contained carcinoma cells in 16 cases and the ilium in 13. In 5 cases the sternum was positive and no specimen was available from the ilium, due either to omission of the procedure or to an unsuccessful tap. Similarly, in 2 cases the iliac crest was positive and no sternal marrow was available. However, from the totals presented it is evident that carcinoma cells from the prostate are found with almost equal frequency in marrow from the manubrium of the sternum as from the crest of the ilium. This lends support to the vascular theory of dissemination of carcinoma of the prostate, as the more important mode of spread, and suggests that the manubrium may be utilized as the routine aspiration site. The latter is of some practical importance as, in these cases, the technique of iliac puncture was more difficult than that of the sternum, especially in cases with metastases with their resultant increased osteosclerosis.

An attempt was made to correlate the degree of malignancy and the presence of distant metastases. The pathological tissue sections were graded* using the criteria suggested by Broders[2]. Carcinoma of the prostate does not readily lend itself to grading because of the wide variation from one area to another in the same section. For our purpose the most malignant area of each section was selected for the grade number, which was based primarily on the differentiation of the acini but with anaplasia and mitotic figures also taken into consideration. In our study, 2 cases were Grade 1 with no evidence of metastases; 17 cases of Grade 2 with 7 showing metastases; 19 cases of Grade 3 with 8 having metastases; and 4 out of 7 cases of Grade 4 showing metastases. We found no specific correlation except that the cases in Grade 1 did not have metastases. As only 2 cases fell into this category, no conclusions are justified.

The blood hemoglobin level of 2415 adult male patients admitted to the University of Iowa Hospitals ranged from 9.2 to 16.9 gm. per 100 cc. of blood[1], averaging 13.4 gm. We chose a hemoglobin level of 10.5 gm. as an

* We are indebted to Dr. J. R. Carter, Associate Professor of Pathology, for reviewing these slides.

arbitrary limit of anemia for the analysis of this group of patients.

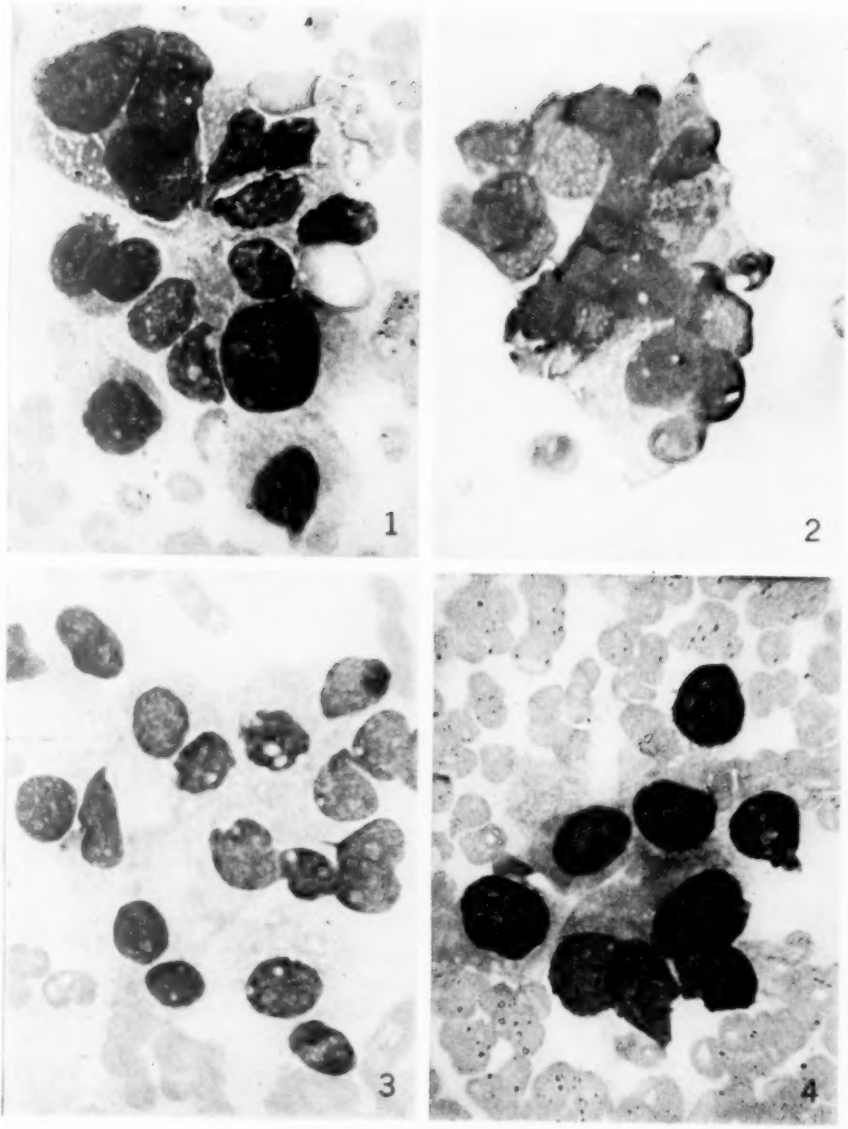
Hemoglobin of 10.5 gm. or less per 100 cc. of blood was frequently associated with bone metastases. There was no clear relationship between the occurrence of anemia and the severity of the metastases. In the anemic group, 5 of 13 patients had widespread skeletal dissemination as determined from roentgenographic examination; but, 5 patients in the non-anemic group were so affected. Because of the wide difference in the numbers of the two groups and due to the fact that complete bone surveys were not done on all patients, the significance of this relationship is uncertain. Eleven patients with anemia had bone metastases, while 17 non-anemic patients had them. Uremia was found only in 3 non-anemic patients. This agrees with the work of Shen and Homburger[9], who found 48% of 50 patients with osseous metastases from all types of primary carcinoma to be anemic. This, coupled with the observation that on the marrow slides of even the most severe cases there were merely isolated clumps of carcinoma cells surrounded by relatively normal hemopoietic tissue, makes us doubt the validity of the hypothesis that the anemia associated with metastatic carcinoma is the result of displacement of normal marrow elements by these foreign cells. We agree with Shen and Homburger[9] and with Vaughan[10] that this anemia is due to some as yet unidentified toxic substance or to a deficiency of necessary hemopoietic material[9]. Uremia was not a factor in the production of anemia in these cases.

If the term leuko-erythroblastic anemia be defined as anemia accompanied by immature elements of the erythroid and myeloid series in the peripheral blood, we found only 5 such cases in the present series (Table 1, Numbers 3, 11, 29, 37, 46). One additional case (No. 28) had 2 of the 3 requirements but lacked immature erythrocytes in the peripheral blood. Like Rundles and Jonsson[6], we found this type of blood picture, generally, with the most severe degrees of anemia. Three patients (Numbers 1, 16, 23), however, had immature granulocytes or immature erythrocytes or both in the peripheral blood without anemia. All 3 had positive bone marrow smears, and 1 had positive roentgenograms. As evidence that invasion of the bone by metastatic carcinoma does not necessarily produce anemia or a leuko-erythroblastic blood picture, 10 patients had bony spread without significant alteration of the formed elements in the peripheral blood.

In the present group, 15 patients had a leukocyte count greater than 10,000 cells per cubic millimeter of blood without a temperature above 99°F. or other discernible conditions predisposing to high white-cell counts. Metastases to bone were apparent in 7 but the complete picture of leuko-erythroblastic anemia was not found, though 3 were anemic and 2 others had more than 1% myelocytes in the peripheral blood. As 19 patients had bone metastases with normal white cell counts, leukocytosis *per se* is not a reliable aid in any given case.

Eight patients were receiving stilbestrol at the time of the bone marrow studies, and 5 had bone invasion. The effect of therapy on metastases has been reported[3].

A close correlation was found between phosphatase activity and metastases (Table 3). Of the 28 patients with proved metastases, acid phosphatase was elevated in 15, normal in 9, and in 4 determinations were not available. Alkaline phosphatase was elevated in 17, normal in 6, and 5 determinations were not done. However, in only 3 patients (Table 1, Numbers



Figs. 1–4.—Clumps of metastatic carcinoma cells from prostate in bone marrow aspiration. Marked morphological variation is shown in these 4 cases.

TABLE 3.—PHOSPHATASE ACTIVITY IN 57 CASES OF CARCINOMA OF THE PROSTATE

	Acid	*Alkaline*
Demonstrated Metastases (28 patients)		
Elevated phosphatases	15	17
Normal phosphatases	9	6
No phosphatase determinations	4	5
Without Metastases (29 patients)		
Elevated phosphatases	1	4

14, 33, 52) were both normal acid and alkaline levels associated with skeletal lesions; one had been receiving stilbestrol, which may well account for the normal phosphatase level. Four had elevated alkaline, and one elevated acid phosphatase levels without evidence of metastases (Table 1, Numbers 2, 9, 10, 22, 44). In this series increased phosphatase activity provided a good indication of bone metastases, though a normal level did not exclude metastases.

Discussion. Our aim in this study was to determine whether or not bone metastases of carcinoma could be detected by bone marrow aspiration with sufficient frequency and facility to use it as a routine procedure. In our 57 cases of carcinoma of the prostate approximately 9% had carcinoma cells in the bone marrow without other diagnostic evidence of this spread. Carcinoma cells were found with almost equal frequency in marrow from the sternum and from the iliac crest; and, with due regard for the diagnostic criteria, they are readily distinguished from normal marrow elements.

Our criteria for tumor cell identification are roughly those outlined by several other authors[4,5,6]. We believe that it is very hazardous to attempt identification of metastatic carcinoma from a single cell, as the tumor cells resemble primitive marrow reticulum cells. In our experience, cells from prostatic carcinoma appear in clusters, usually forming a syncytium. The individual cells vary in size but are predominantly large. The nuclei are relatively large and round or oval, though occasionally pleomorphic. Nuclear chromatin is a heavy reticulum surrounding 2 or 3 very distinct nucleoli. The cytoplasm varies in color from moderately basophilic to pale gray or blue. It is mottled, vacuolated, and has indefinite irregular borders. Figures 1 to 4 are color photomicrographs of typical examples of these cells.

A multinucleated marrow cell (probably an osteoclast) which might be mistaken for a clump of neoplastic cells is shown in Fig. 5. The nuclei, which are frequently piled upon each other, are round or ovoid and contain two or more distinct nucleoli. The chromatin is a spongy reticulum. Fine azurophilic granules are dispersed through the pale blue-gray cytoplasm. This cell is rarely encountered in normal marrow, being most often encountered in hypoplastic marrow. It was not unusual to find 5 to 6 osteoclasts in a marrow smear from patients with prostatic carcinoma when few other marrow elements were present.

Occasionally a nest of plasmocytoid cells was encountered on smears of marrow aspiration which resemble carcinoma cells. A clump of these cells is shown in Fig. 6. The cytoplasm, mottled and often vacuolated, is moderately basophilic in color, and a perinuclear halo is usually present. The cytoplasm does not form a syncytium, but rather each cell can be distinguished as an individual. The cell borders are usually ragged and irregular. The nucleus is eccentrically placed, appears immature with several distinct nucleoli, and its

chromatin forms a fine reticulum. We found clumps of these cells and single cells in normal and various pathological conditions. The photomicrograph was taken from a marrow smear of a 13-year old girl with congenital hypoplastic anemia.

ent seemed unlikely to have been produced by compression from these foreign cells.

Since both sternal and iliac crest punctures are not necessary in these cases, the time consumed by the bone marrow survey can be roughly halved.

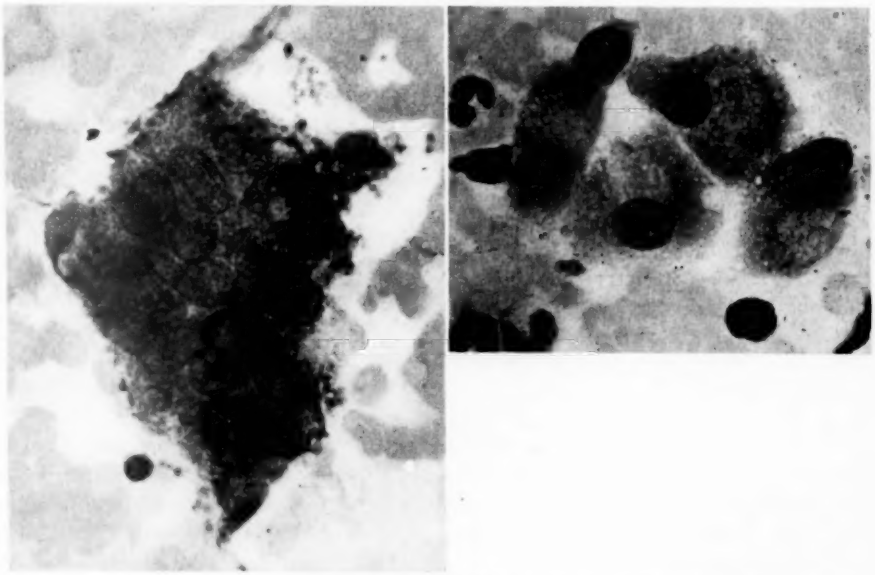


FIG. 5.—A bone marrow giant cell (osteoclast) that may be confused with a clump of neoplastic cells.

FIG. 6.—A nest of plasmocytoid cells in bone marrow that may be mistaken for metastatic carcinoma.

Although complete differential counts were not done on the marrow films, we did not detect any significant variation in the frequency distribution of the normal cells. Eosinophilia was noted in 4 cases. Two of these were positive for carcinoma cells. Usually cellularity was normal; however, some appeared hypocellular and others hyperplastic. Even though a marrow slide might be "well loaded" with carcinoma cells, most often such a preponderance of blood-forming elements was evident that any anemia which might be present seemed unlikely to have been produced by compression from these foreign cells.

Since both sternal and iliac crest punctures are not necessary in these cases, the time consumed by the bone marrow survey can be roughly halved. Thus, 8 slides can be prepared from any one of these sites and scanned within an hour. At least this number of slides should be examined before calling a given aspiration negative, for in only 9 of our 19 cases with positive aspirations were carcinoma cells found on all 8 slides. In several cases they were present only on 1 or 2 slides from one or the other area.

Leuko-erythroblastic anemia did not occur with as great frequency as anticipated. Of the 5 cases only 1 did not have positive roentgenograms. All cases

with a significant percentage of immature granulocytes or erythrocytes in the peripheral blood had proof of metastases. However, many patients had metastases without disturbance of peripheral blood pattern. The presence of leuko-erythroblastic anemia is indicative of bone dissemination but its absence does not exclude metastases.

Lack of correlation between the grade of malignancy of the primary tumor and the occurrence of metastases was not particularly surprising. The comparison was of interest for it has not been reported previously utilizing the method of this study. The inherent difficulties in exact grading of prostatic carcinoma have been discussed.

Among the adjunctive studies the phosphatase activity was the most helpful. In only 2 patients (untreated with stilbestrol) were metastases demonstrated in the absence of increased phosphatase levels; and in only 5 patients were there elevated phosphatases without evident metastases. Whether the relationship of phosphatases will hold for other types of metastatic carcinoma remains to be seen.

Summary and Conclusions. We studied 57 cases of carcinoma of the prostate, 49 of which were proved. Data included skeletal roentgenograms, bone marrow aspirations from iliac crest and sternum, peripheral blood picture, grading of pathological specimens according to Broder's[2] classifications, acid phosphatase, alkaline phosphatase, blood urea nitrogen, and creatinine. The following conclusions are drawn:

1) Cells metastatic from carcinoma of the prostate were demonstrated in "routine" bone marrow aspirations in 33%.
2) These cells occurred with equal frequency in marrow from the sternum and the ilium.
3) Approximately 9% had widespread skeletal dissemination of carcinoma without diagnostic evidence other than positive bone marrow punctures.
4) Adjunctive laboratory studies, such as peripheral blood smears and phosphatases, were helpful but not diagnostic. The alkaline phosphatase was the most useful of these.
5) We found no correlation between the presence of metastases and the Broder's grade of malignancy of the primary carcinoma.
6) Since an adequate bone marrow examination can be performed in one hour or less by competent persons, it should be done in patients with prostatic carcinoma being considered for radical surgery.

REFERENCES

1. **Barer, A. P.**: Personal communication.
2. **Broders, A. C.**: S. Clin. North America, **21**, 947, 1941.
3. **Flocks, R. H., Harness, W. N., Tudor, J. M.,** and **Prendergast, L.**: Trans. Southcen. Sect., Am. Urol. Assn., September, 1950.
4. **Leitner, S. J.**: Bone Marrow Biopsy, Grune and Stratton, 1949.
5. **Rohr, K., and Hegglin, R.**: Deutsch. Arch. f. klin. Med., **179**, 61, 1936.
6. **Rundles, R. W.,** and **Jonsson, U.**: Am. J. Med. Sci., **218**, 241, 1949.
7. Idem: Blood, **6**, 16, 1951.
8. **Selberg, W.**: Deutsch. Arch. f. klin. Med., **190**, 380, 1943.
9. **Shen, S. C.,** and **Homburger, F. H.**: J. Lab. & Clin. Med., **37**, 182, 1951.
10. **Vaughan, J. M.**: J. Path. & Bact., **42**, 541, 1936.

THE DETERMINATION OF THE STATISTICALLY MINIMUM NUMBER OF CASES

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There is considerable advantage to be obtained from statistical scrutiny of the reports of medical research. A good part of this advantage is lost for one of three obvious reasons. In the first place, a large proportion of the readers do not understand statistical terminology; consequently authors hesitate to publish their results in statistical parlance. In the second place, some techniques are difficult to carry out as well as difficult to understand, and authors do not expend the required time and effort. In the third place, statistical scrutiny frequently shows the work being described to be much weaker than the author's convictions, and the author, therefore, prefers to ignore statistical interpretation, since he, himself, has slight confidence in statistical approbation.

This state of affairs is being gradually overcome, and much recent literature is replete with statistical analyses. Nevertheless, some short-cut method, which can be applied to past publications as well as present research, needs to be devised. Such a method must attain certain specific aims. It must be simple enough to be applied by uninitiated readers; it must be based upon recognized statistical techniques; it must be applicable to nearly every type of research reporting; and it must be capable of helping the reader to discern between incomplete reporting or inadequate subject material, and satisfactory completion of research.

To devise a technique that is at once simple enough for an unsophisticated reader and adequate to a critical statistician may seem an impossible task. It is with some misgivings, therefore, that the author makes the present proposal. It is believed, however, that the method here described leads fairly close to such ideal qualities.

Our method is derived from the chi-squared treatment of the double dichotomy which leads to the mathematical prediction of the probability of a denial of the null hypothesis[1]. This statement may seem to the reader to be esoteric and incomprehensible. Therefore, we must define and describe the above terms. Chi-squared refers to a method of estimating the proportional areas of the normal bell-shaped distribution curve of biological variation. A double dichotomy is the division of the data included in experimental results into 2 sets of 2 classes each. The 2 sets may be experimental and control series or cases, they may be 2 different sets of experimental studies, or they may be a real set and an imaginary or presumed set of normally expected results or data. The 2 classes of each set are, for instance, success or failure, large or small, above average or below average, or they may be the surviving and perished cases. It is essential that these 4 divisions be mutually incompatible, that is, there cannot be indecision in the classification. Thus a single case or datum may be experimental or control, and either alive or

dead. The null hypothesis is the presumption, for the sake of argument, that the results could have occurred by accident or chance. If it can be shown that the results are not accidental, then and only then can the results be attributed to the experimental treatment.

To disprove the null hypothesis, certain mathematical manipulations are undertaken upon the data to predict the probability of a chance result. When this probability can be shown to be sufficiently slight, the statistician concedes that the experimental results may be useful. It is usually sufficient to show that the results are not more than 5% chance, that is, that there is about a 20 to 1 bet in favor of a real association. This is called the 5% level of confidence. Occasionally, the 1% level of confidence may be preferred.

Now, this computation of chance association depends upon 3 variables, when applied to the double dichotomy. Firstly, the more cases that are studied, the more remote becomes the element of accident or chance: hence, the ever-crying demand for more and more cases. But numbers alone cannot lend credence to data, for, secondly, chance association depends upon the relative difference between the two classes of the dichotomy. When the data are divided into nearly equal classes, more cases are required than when either success (or failure) is relatively rare. Thirdly, the greater the relative difference between these classes, for the 2 sets of the dichotomy, the fewer cases are required. The reader can see, therefore, that no nice round number for the least number of cases can be predetermined. As will appear in the table below, there are experiments when as few as 2 cases are needed, and others where at least 3500 are required for each set of data.

The double dichotomy is presented in a certain exact form for the application of this statistical technique. Each item must be exactly known, or inferred, from the reported data. This form is shown in Table 1. When the values of the dichotomy are known, the probability for chance can be computed. However, the corollary is also true, with certain assumptions, that for a given probability of chance, and given relationships between the proportions a, b, c, and d, the values of N_1 and N_2 can be predicted.

This is what has been done. Table 2 gives the relationship, or ratio, of e:f, and the disproportion or difference, delta ($\triangle$). We have computed the necessary values for N_1 or N_2, which ever is the lesser. Actually, the computation was carried out for $N_1 = N_2$, but this need not affect the application of the table to real data, it only serves to render the interpretation more conservative.

TABLE 1.—MATHEMATICAL FORM FOR THE PRESENTATION OF DATA IN A DOUBLE DICHOTOMY

	Success	*Failure*	*Number of Cases*
Experimental	a%	b%	N_1
Control	c%	d%	N_2
Average	e%	f%	
Difference	$\triangle$		

a and b are percentages of N_1
$a + b = 100\%$
c and d are percentages of N_2
$c + d = 100\%$
e is the arithmetic mean (average) of a and c
$(a + c) \div 2 = e$

f is the arithmetic mean (average) of b and d
$(b + d) \div 2 = f$
$e + f = 100\%$
$\triangle$ is the difference between a and e
$\triangle = (a - e)$

TABLE 2.—TABLE FOR THE MINIMUM NUMBER OF CASES IN THE SMALLER HALF OF A DOUBLE DICHOTOMY

Computed for the condition that p = 5%, for various disproportions; for p = 1%, double the number of cases.

Value of △ (%)	*Values of the ratio e:f (in per cent)*									
	50:50	*40:60*	*30:70*	*25:75*	*20:80*	*16:84*	*13:87*	*10:90*	*8:92*	*6:94*	*5:95*
1	3500	3400	3000	2700	2250	1900	1600	1260	1050	780	660
2	880	840	740	660	560	470	400	320	260	200	168
3	390	380	330	295	250	210	175	140	115	88	73
4	220	215	188	168	140	120	96	78	65	49	42
5	140	135	118	106	90	75	64	50	42	32	27
6	97	95	82	74	63	54	49	35	29	22	
8	55	54	47	41	35	29	25	20	16		
10	35	34	30	27	23	20	17	13			
12	25	24	21	19	16	14	12				
15	16	15	14	12	10	9					
20	9	9	8	7	6						
25	6	6	5	5							
30	4	4	4								
40	3	3									
50	2										

The application of the table can be best shown by example. Two such examples are quoted. In the first, a study was made of the usefulness of hyoscine in reducing the incidence of seasickness[3]. The author reported 34 cases of seasickness among 125 men who received hyoscine, and 63 cases of seasickness among 118 who received placebos. These data are put into the tabular form of the double dichotomy, in Table 3. We find that e:f = 60:40, and that △ = 13%. From Table 2, in the 40:60 column, at the 12% value for △, we find the number 25. This means that at least 25 men must have been measured to disprove chance results. Since the smaller actual number is 118, there are sufficient data. Had we desired the 1%-level of confidence, 25 must be doubled, and 50 men would be required. There are still enough cases.

As a second example, consider a report on sulfa-drugs, used in treating lobar pneumonia[2]. With the use of sulfapyridine, there were 72 deaths in 733 cases, and with sulfathiazole, 54 deaths in 447 cases (Table 4.) Again, the data are reduced to the dichotomy form, as in Table 3. From Table 2, at e:f = 90:10 (or 10:90) and △ = 1% at least 1260 cases are required. The smaller number, 447, is less than ½ of the required number. Therefore, although over 1000 cases in all are reported, it cannot be shown that the results are not accidental. Therefore, these data do not establish a superiority for sulfathiazole in the treatment of lobar pneumonia.

TABLE 3.—SEASICKNESS DATA REDUCED TO A DOUBLE DICHOTOMY (TYLER[3])

	(Success) Not Seasick	*(Failure) Seasick*	*Number of Cases*
Experimental (hyoscine)	100% − 27% = 73% (a%)	34/125 = 27% (b%)	125
Control (placebo)	100% − 53% = 47% (c%)	63/118 = 53% (d%)	118
Average	(73 + 47) ÷ 2 = 60% (e%)	(27 + 53) ÷ 2 = 40% (f%)	
	△ = 73 − 60 = 13% (a% − e%)		

TABLE 4.—DATA ON SULFA-DRUGS IN PNEUMONIA REDUCED TO A DOUBLE DICHOTOMY (FLIPPIN[2])

	Survivors	*Deaths*	*Cases*
Sulfapyridine	$100\% - 9.8\% = 90.2\%$ (a%)	$72/733 = 9.8\%$ (b%)	733
Sulfathiazole	$100\% - 12.1\% = 87.9\%$ (c%)	$54/447 = 12.1\%$ (d%)	447
Average	89.05% (e%)	10.95% (f%)	

$\triangle = 1.15\%$ (a% − e%)

Although this proposed statistical tool must remain an approximation, it is the author's conviction that we have here a rather simple and direct method of testing data. It can be applied to old as well as to new data, with only a little ingenuity in devising the dichotomy. It will serve to establish when insufficient data are presented in old data, and will serve to predict the required extent of new research, once the proportions of a, b, c, and d, have been approximately determined.

Summary. A method is presented which permits experimental data to be reduced in a simple manner to a form from which their statistical significance can be determined. No difficult mathematics and no abstruse concepts are required. The method is equally as applicable to new as to already published data.

REFERENCES

1. **Arkin, H.,** and **Colton, R. R.**: An Outline of Statistical Methods, p. 109; New York: Barnes and Noble, Inc., 4th Ed., 1939.
2. **Flippin, H. F.**: J. Am. Med. Assn., **121**, 230, 1943.
3. **Tyler, D. B.**: Am. J. Physiol., **146**, 458, 1946.

PLASMA SODIUM AND POTASSIUM CONCENTRATIONS IN CONGESTIVE HEART FAILURE. RELATIONSHIP TO PATHOGENESIS OF FAILURE*

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Although retention of salt and water had long been recognized in congestive failure, the possible role of the kidney in the pathogenesis of cardiac edema was first emphasized in 1944 by Warren and Stead[22]. These investigators postulated the following chain of events: (1) inadequate cardiac output, (2) alteration in renal hemodynamics with resulting excessive retention of salt and water, (3) consequent increase in plasma volume and concomitant accumulation of interstitial edema, and, finally, (4) rise in venous pressure. This hypothesis stimulated intensive investigation of renal hemodynamics in normal subjects and in cardiac patients. Increased tubular reabsorption of sodium without significant change in glomerular filtration has been demonstrated subsequently in normal subjects as the result of exercise[11], change from a recumbent to a standing or sitting position[11,15], venesection[15], elevation in renal venous pressure[8], and venous stasis in the extremities[8]. Exaggerated renal retention of sodium occurs in heart disease, as exemplified by the fact that much lighter exercise provokes a much greater tubular reabsorption of sodium in the cardiac patient than in the normal control[18]. Sodium retention by the cardiac patients was also demonstrated in the absence of changes in renal hemodynamics[18]. Furthermore, evacuation of sodium and water may take place during recompensation without any changes in glomerular filtration rate or renal plasma flow[2].

The fact that changes in renal hemodynamics are unnecessary for the increased tubular retention of sodium in congestive failure or for the tubular rejection during recovery directs attention to the possibility of a fundamental disorder of extrarenal sodium metabolism. If sodium retention were primary, a rise in plasma sodium con-

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centration would be anticipated during the development of congestive failure. Data on plasma sodium levels in congestive failure are meager and the present status does not differ from that in 1948, so aptly characterized by Peters[17] as follows, "The problem of plasma sodium concentration has been more discussed than investigated." Recent reports have been inconclusive, either because of the administration of mercurial diuretics to most of the patients prior to blood sampling[12,17,20], or because of lack of information on the use of these agents[9,12]. This constituted a serious omission, in view of the known tendency for mercurial diuretics to produce hyponatremia[3,20]. The findings of other workers will be analyzed in the discussion of the results from the determination of plasma sodium levels in untreated congestive failure to be reported in this study.

The demonstration of cellular uptake of potassium during recovery from congestive failure[10,18], suggested cellular loss of this element during decompensation and thus prompted a study of plasma potassium concentration in untreated cardiac failure.

The relationship of the findings to the pathogenesis of congestive heart failure will also be discussed.

Method and Material. Plasma sodium and potassium concentrations were determined in 71 cases of congestive failure uncomplicated by renal disease or by vomiting or diarrhea. Samples were drawn soon after admission and before any mercurial therapy in 56 of the 71 patients. None of these had received mercurial diuretics for at least 2 weeks prior to admission. These patients, therefore, represented congestive heart failure cases uncomplicated by renal, extrarenal, or therapeutic factors. Plasma samples in the remaining 15 cases were drawn after a variable period of hospitalization. During the fortnight before plasma samples were obtained, 9 had received 1 to 2 mercurial injections, 5 had received 3 to 4 parenteral doses, and 1 had received 8 injections.

The cases were divided into 4 groups, depending on whether right-sided or left-sided failure was predominant. Group I consisted of 12 cases with severe right-sided failure, but little or no left-sided failure. Group II comprised 17 cases with severe pulmonary congestion and edema, but little or no peripheral edema. Group III included 26 cases with severe right and left-sided failure. Group IV comprised 16 cases with mild to moderate right and/or left-sided failure.

Repeat determinations for plasma sodium and potassium levels were obtained after recompensation from heart failure in 26 cases. Serial levels were obtained and correlated with change in weight in 6 cases. After restoration of compensation in 4 of the latter, congestive failure was induced by sodium chloride supplements and/or ambulation, while under constant observation in the hospital.

Plasmas were analyzed for sodium and potassium concentrations on the flame photometer, according to the method described previously[14]. Normal values were obtained from a series of 73 normal fasting adults[19]. Body weight was accurately measured on the Troemer beam balance.

Results. Table 1 summarizes the values obtained for plasma sodium and potassium concentrations in congestive heart failure and compares the mean and the distribution of values with the normal. In Figure 1 the individual values for sodium and potassium in each of the 71 cases are depicted graphically. The classification according to type of congestive failure, presence or absence of azotemia and antecedent mercurial therapy is indicated for each case by appropriate symbols.

PLASMA SODIUM CONCENTRATION. The over-all mean of 149.0 ± 7.2 mEq./L. in the 71 cases of congestive failure was definitely higher than the normal mean of 142.0 ± 3.1 mEq./L. The mean values were equally elevated for patients in Group I with severe right heart failure, Group II with severe left heart failure, and Group III with combined right and left failure, but were not quite as high for those in Group IV with mild to moderate failure. The mean value for the 18 pa-

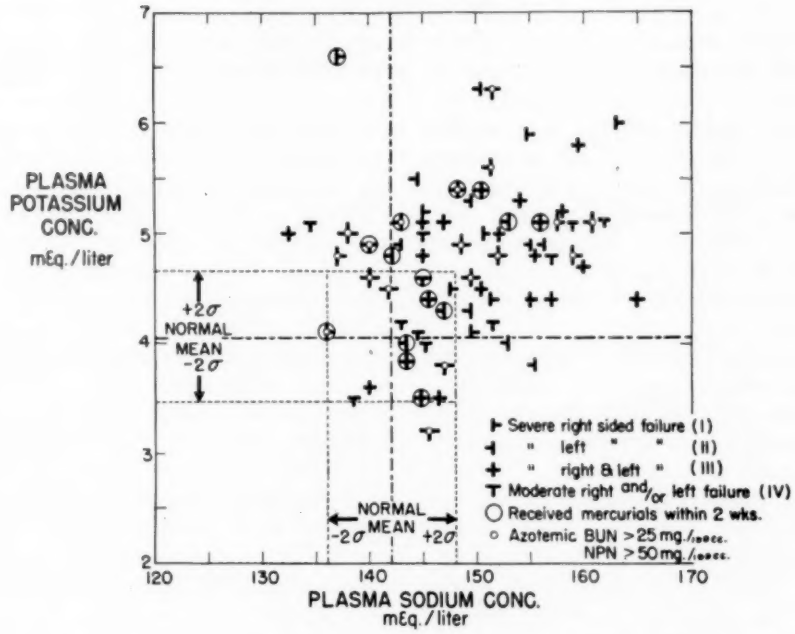

FIG. 1. Plasma sodium and potassium concentrations in congestive heart failure.

TABLE 1.—PLASMA SODIUM AND POTASSIUM CONCENTRATIONS IN CONGESTIVE HEART FAILURE. MEAN VALUES AND DISTRIBUTIONS COMPARED WITH THE NORMAL

		Congestive Heart Failure				
	Normal Controls	*All Cases*	*Group I*	*Group II*	*Group III*	*Group IV*
No. of cases	72 (Na) 73 (K)	71	12	7	26	16
Plasma Na mean mEq./L	142.0	149.0	149.2	150.2	149.3	147.0
Std. dev. (σ)	±3.1	±7.2	±8.6	±5.7	±7.3	±7.1
% of cases above normal mean	50*	85	75	100	85	75
below normal mean	50	15	25	0	15	25
% of cases above $+2\sigma$	3*	54	58	65	58	31
between $\pm 2\sigma$	94	44	42	35	38	63
below -2σ	3	2	0	0	4	6
Plasma K mean mEq./L	4.06	4.8	5.0	4.8	4.7	4.5
Std. dev. (σ)	±0.32	±0.7	±0.7	±0.6	±0.6	±0.7
% of cases above normal mean	50*	85	100	82	85	75
below normal mean	50	15	0	18	15	25
% of cases above $+2\sigma$	3*	59	67	65	62	44
between $\pm 2\sigma$	94	39	33	35	38	50
below -2σ	3	2	0	0	0	6

* Theoretical normal distribution

tients with azotemia (as indicated by blood urea nitrogen over 25 mg./100 cc. or blood non-protein nitrogen over 50 mg./100 cc.) was 147.0 mEq./L., and was thus slightly but not significantly reduced. The mean plasma sodium concentration in the 15 patients who had received mercurial therapy during the 2 weeks before blood sampling was 143.2 mEq./L., a figure substantially lower than the mean for the entire series.

Eighty-five per cent of all cases had sodium values above the normal mean and each of the individual groups likewise showed a preponderance of values above the normal mean. The majority of cases in Groups I, II, and III had plasma sodium concentrations greater than 2 times the standard deviation above the normal mean, indicating the likelihood of the plasma level to exceed the upper limits of normal range in severe congestive failure. In Group IV with mild to moderate failure, only about one-third of the patients had values above this level.

Eleven of the 71 patients (15%) had plasma sodium concentrations below the normal mean and 2 of these had values below the normal range. Neither of the 2 patients with definite hyponatremia had azotemia or mercurial therapy during the fortnight prior to withdrawal of the specimen.

A graphic representation of initial plasma sodium levels during failure and final levels after compensation is given for 26 cases in Figure 2. The initially high plasma sodium concentration fell significantly in 20 cases, to final levels that were slightly above normal in 5 cases, to within the normal range in 13 and below normal in 2. The mean sodium concentration in this group at the height of failure was 152.8 mEq./L. and after recompensation, 143.9 mEq./L. The average fall was 8.9 mEq./L., the greatest magnitude of fall occurring in cases with initially high concentrations of sodium. Six of the 26 cases showed a slight rise in plasma sodium concentrations from an essentially normal mean of 142.4 to a mean of 145.7 mEq./L. The average rise was only 3.3 mEq./L.

Figure 3 depicts the course of the body weight and plasma sodium concentration during recovery from cardiac decompensation in 6 patients and during a subsequent attempt at induction of congestive failure by sodium chloride supplements with or without ambulation in 4 of these patients. An essentially parallel fall in plasma sodium level and body weight during recovery from congestive failure was observed in 3 patients (M. H., J. J., and L. K.); maintenance of plasma sodium concentration at an abnormally high plateau until all edema had been evacuated was observed in 3 patients (J. T., K. B., and J. D.). The plasma sodium level fell sharply after stabilization of body weight at its minimum in each of these patients, despite concurrent administration of sodium chloride supplements to one patient (J. D.).

Continued administration of the salt supplements to patient J. D. led subsequently to a rise of plasma sodium almost to its original level, along with a small weight gain. Sodium chloride supplements in another patient (L. K.) were followed by a progressive rise in both plasma sodium concentration and body weight to their original levels. The addition of sodium chloride to the diet of another patient (J. J.) did not interfere with restoration of compensation while strict bed rest was maintained, but was accompanied by a slight rise in plasma sodium level and a gain in weight after ambulation was permitted. Institution of ambulatory activity in patient M. H. during maintenance on a low sodium diet was followed by a significant rise in

plasma sodium concentration from a low to a normal level and a slight gain in weight; addition of 6.0 gm. salt to the daily diet without modification of physical activity led to an abrupt development of hypernatremia with a slight gain in weight; confinement to and/or ambulation leads to accumulation of relatively greater quantities of sodium than water in the extracellular compartment.

PLASMA POTASSIUM CONCENTRATION. The over-all plasma potassium concentration in congestive heart failure

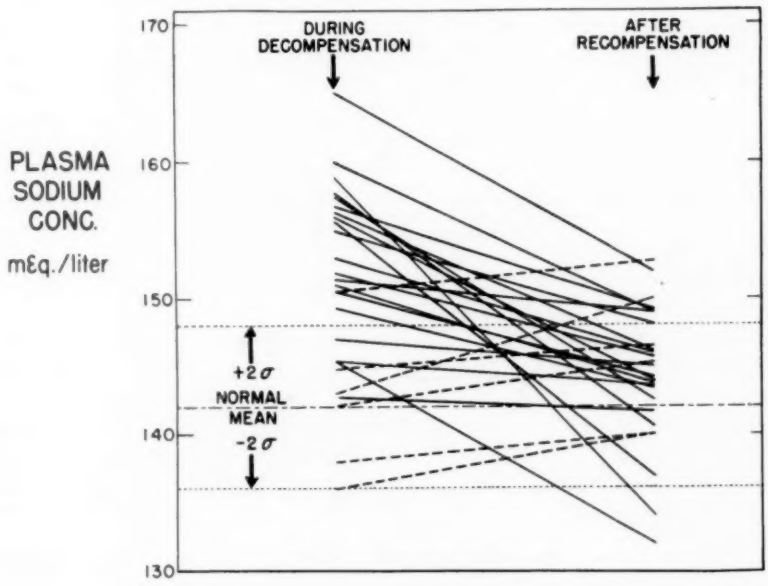

FIG. 2. Plasma sodium concentrations during cardiac decompensation and after recompensation in 26 patients. Twenty patients showed a fall (straight line) and 6 showed a rise (broken line) in concentration with recompensation.

bed with maintenance of salt supplements was followed by an abrupt fall in plasma sodium level, but a continued gain in weight; resumption of a low sodium diet resulted in return of plasma sodium level to normal and a slight weight loss. The dramatic changes in plasma sodium concentration in patient M. H. and the rise in plasma levels in the other 3 cases indicates that induction of congestive failure by sodium chloride supplements was 4.8 ± 0.7 mEq./L. compared to the normal mean of 4.06 ± 0.32 mEq./L. Group I had the highest mean and Group IV, the lowest mean among the separate groups. Considerably more patients (85%) had values above than below the normal mean. This disproportion was found in each of the separate groups, but was least apparent in Group IV. A significant number of patients (59%) had values greater than the mean plus twice its standard de-

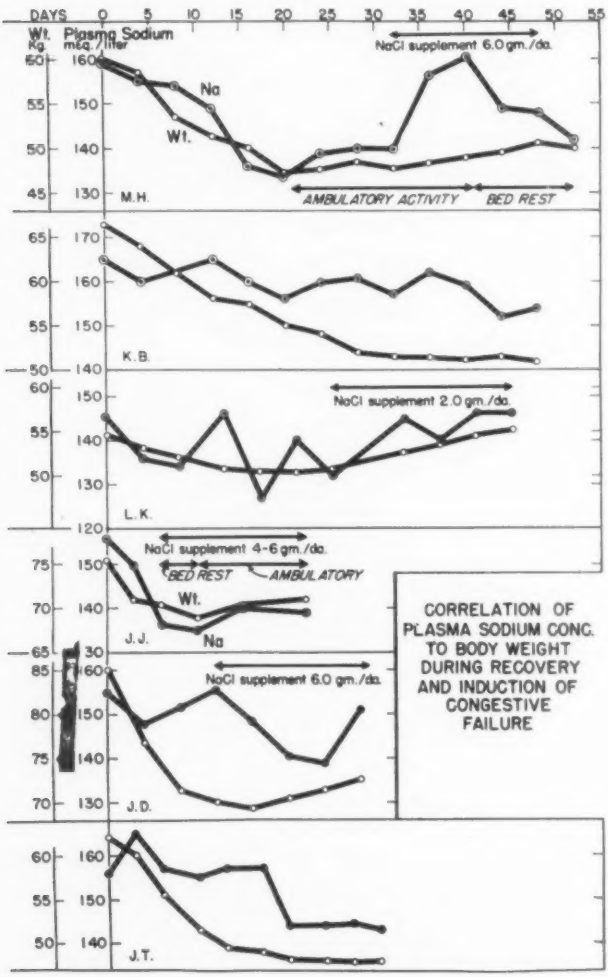

FIG. 3. Correlation of plasma sodium concentration to body weight during recovery and induction of congestive failure.

viation. Approximately two-thirds of the patients in each of the first 3 groups, but less than half in Group IV had values above this level. Only 1 abnormally low plasma potassium level was found. This occurred in Group IV.

The mean plasma potassium concentrations in patients who had received mercurial injections and in patients who were azotemic were 4.7 and 4.8 mEq./L., respectively, and thus did not differ from the mean of the entire series.

The mean plasma potassium concentration fell slightly in the 26 cases restudied after compensation. There was no correlation, however, between the changes in potassium level and the fall in sodium level as recovery took place.

Discussion. These studies signify that both plasma sodium and potas-

sium concentrations are frequently elevated in congestive heart failure. The absence of significant differences in electrolyte levels among the groups with predominant right-sided failure, isolated pulmonary edema and combined right and left heart failure indicates that the elevations are related to failure of the circulation and release of electrolyte from embarrassed cells as a whole, rather than to localization of the fluid in the pulmonary or systemic compartments. The lack of correlation with blood urea nitrogen levels indicates that abnormalities in electrolyte concentration are independent of the azotemia that frequently accompanies congestive failure in the absence of demonstrable intrinsic renal disease.

The mean values for plasma potassium of 4.8 ± 0.7 mEq./L. in our 71 cases of congestive failure, as compared with 4.06 ± 0.3 mEq./L. in 73 normal controls, were in general agreement with the findings of Squires, Singer, Moffitt and Elkinton[20], who reported a mean value of 4.62 ± 1.04 mEq./L. in 54 patients with congestive failure, as compared with 4.00 ± 0.33 mEq./L. in 18 normal subjects.

The demonstration of hypernatremia in the majority of our cases is at variance with other reports. In a study of sodium clearance, Mokotoff, Ross and Leiter[13] gave data on plasma sodium concentrations in 16 patients with frank congestive failure. The average value of 134.7 mEq./L. would appear low, according to the usual standards, but exceeded the average concentration of 132 mEq./L. obtained by the same investigators in 13 normal controls and compensated cardiac patients. On the other hand, hyponatremia was found in the majority of cases of congestive failure in 3 other reports[9,12,20].

The major causes of hyponatremia in congestive failure were brought out by Squires, Singer, Moffitt and Elkinton[20] in a well documented series of 54 determinations of plasma sodium on 44 patients with predominant right heart failure. Because of differences in clinical material, their series and that in this report are complementary, making a comparative analysis informative. Ten samples in their series were obtained in patients with intrinsic renal disease or vomiting, complications which, as they recognized, are capable of modifying plasma electrolyte concentration independently of the heart. Since patients with these complications were excluded from our series, those 10 samples have been disregarded in the comparative analysis. The fact that all of their patients had predominant right heart failure, whereas 17 of ours had isolated left heart failure, is probably of little concern, because of the comparability of the plasma sodium levels in these 17 and the remaining 54 cases of our series. Possible differences in the severity of the cardiac failure in the 2 series would be of greater importance, but cannot be evaluated from the data at hand. The major difference in the 2 series lies in the treatment prior to plasma sodium determination. All patients in the Philadelphia series had been receiving low sodium diets and 36 of the 44 samples were obtained after treatment with mercurials, whereas few of our patients had been restricted in sodium intake and only 15 of the 71 had received mercurial diuretics during the fortnight preceding the initial determinations. Squires *et al.* found normal plasma sodium concentrations in 5 of their 8 untreated cases of congestive failure, hyponatremia in 2, very slight elevation in 1, and were quite aware that this group was too small to permit conclusions. On the other hand,

they found hyponatremia in 20 of their 36 patients previously treated with mercurials, normal levels in only 15 and very slight elevation in 1, and thus clearly demonstrated the frequency of hyponatremia in edematous cardiacs who had received mercurial diuretics. The significantly lower plasma sodium concentrations in the 15 patients of our series previously treated with mercurials than in the 56 untreated cases tend to support these conclusions. It would thus appear that differences in the distribution of plasma sodium concentrations in the 2 series are attributable to differences in clinical material.

Fox, Friedberg and White[9] determined plasma sodium concentrations in 26 cases of chronic congestive failure and found hyponatremia in 19, normal levels in 5, and elevation in 2. Their data, as yet published only in abstract form, cannot be analyzed or evaluated, because of lack of information on severity, complications and prior mercurial therapy.

Miller[12] found a mean serum sodium level of 135.2 mEq./L. in 26 patients with congestive failure, as compared with a normal control value of 139.5 mEq./L. He stated that most of his patients had received digitalis and mercurials in the past, but failed to present comparative data for the untreated and treated groups. Nevertheless, he interpreted the hyponatremia as evidence that cardiac edema results from an initial retention of water rather than sodium, despite the fact that most of his patients exemplified therapeutic modifications of congestive failure. He supported his conclusion by balance data obtained on 8 patients during recovery from congestive failure, showing a relatively greater external loss of water than sodium. Miller's balance data confirmed prior reports from the Johns Hopkins Hospital and from our laboratory[18,10]. Calculations of fluid and electrolyte partitioning, made in our previous cases by the method of Darrow[4], revealed that the extracellular compartment lost equivalent amounts of sodium and water in some cases, and slightly disproportionate amounts in others, whereas the cells consistently lost water and gained sodium during compensation. The cellular changes were thus directly responsible for the greater external losses of water than sodium.

The fact that all patients in the 3 studies[10,12,18] lost relatively more water than sodium as they became compensated suggests retention of a proportionately greater quantity of water than sodium during the development of congestive failure, but does not necessarily imply primary retention of water, as postulated by Miller. Our study of changes in plasma sodium concentration and body weight during induction of congestive failure by salt supplements and/or ambulation in 4 patients with heart disease represents the first phase of an attempt to elucidate the sequence of metabolic changes during the development of cardiac edema. The association of a striking rise in plasma sodium concentration with only a very slight gain in weight in patient M. H. was strongly suggestive of initial sodium retention by the kidneys. The rise in plasma sodium level and associated weight gain in the other 3 patients were consistent with initial sodium retention, but could also be explained by primary water retention accompanied by cellular uptake of water and release of sodium. Studies of water, sodium, potassium, and chloride balance during the induction of congestive failure, which are in progress, should aid in the clarification of this problem.

The fall from high towards normal plasma levels of sodium observed in

most cases followed during recovery from congestive failure represents the expected trend in the correction of an abnormality. A similar trend of lesser magnitude was an incidental finding in the study of Briggs *et al.*[2], who reported a mean plasma sodium concentration of 140.9 mEq./L. in 14 patients in congestive failure and a mean value of 138.0 mEq./L. in the same patients after compensation.

The plasma sodium concentration in patients with congestive failure may deviate in either of 2 directions; it may rise above normal limits, as shown by our studies, or it may fall to subnormal levels, generally as a complication of mercurial diuretics, but occasionally in the absence of administration of such agents. The elaboration of a theory for the development of congestive failure, which will account for the frequent finding of hypernatremia and the occasional finding of hyponatremia in untreated cases remains for consideration.

The magnitude of the elevation of plasma sodium concentration in many of our cases indicates a significant rise in the osmolarity of the extracellular fluid. This, in turn, probably reflects a rise of osmolarity within the cells, since adjustments in extracellular fluid must take place in order to maintain osmotic equilibrium across the cell membrane. This is in accord with the hypothesis set forth in a previous communication from this laboratory[10] and recently advanced independently by Squires, Crosley and Elkinton[7,21] that circulatory insufficiency causes an alteration in cellular metabolism manifested by liberation of base from osmotically inactive constituents of the protoplasm. A rise in cellular osmolarity would lead to the transfer of sodium and potassium into the extracellular compartment and cellular uptake of water, which apparently accompany the development of congestive heart failure.

During the period of circulatory insufficiency when the metabolic needs of the cells are not fulfilled, the necessity of maintaining a high osmotic tension in the extracellular fluid equal to that in the cells may supply the stimulus for renal retention of sodium, and the necessity of diluting the osmotic constituents of the cells may provide the stimulus for the retention of water. The stimuli may be extrarenal and mediated through either humoral[6] or hormonal[1,5,16], factors. The possible influence of the latter agents is suggested by the demonstration of increased adrenal corticoids[5,16] and antidiuretic hormones[1] in the urine of patients in congestive failure. On the other hand, the mechanism by which increased reabsorption of sodium and water is accomplished may be intrinsic within the renal tubular epithelium and referable to cellular changes analogous to those postulated for the body as a whole.

Circulatory insufficiency in the cardiac patient during exercise would presumably cause the postulated rise in cellular osmolarity, the transfer of sodium and potassium into the extracellular compartment, the cellular uptake of water, and the renal retention of sodium and water and loss of potassium. These changes apparently accompany the development of congestive failure and would be expected to lead to a rise in plasma sodium concentration. Complete recompensation during rest would then be accompanied by decrease in cellular osmolarity to normal with osmotic inactivation of cellular base, cellular uptake of sodium and potassium, cellular release of water, and excretion of this water and the accumulated sodium, but with retention of potassium. Under these circumstances, plasma sodium

concentration would return to normal and edema would be evacuated. Incomplete recompensation, on the other hand, would leave an elevated cellular osmolarity and permit transfer of only part of the water out of the cells and only part of the lost potassium and perhaps sodium back into the cells. Evacuation of retained water and sodium from the extracellular compartment would also be incomplete, resulting in formation of edema with persistence of an elevated plasma sodium concentration. Repeated episodes of exercise and rest may gradually deplete cellular electrolytes without eliminating the excess cellular water and thus eventually may reduce cellular osmolarity below normal with consequent lowering of extracellular osmolarity by the development of hyponatremia. This would be especially prone to occur with the administration of mercurials or other agents that promote the excretion of electrolytes or with an inadequate dietary intake to replenish cellular losses. Reduced cellular osmolarity during rest, accounting for the occasional cases with hyponatremia, would not preclude the possibility of a rise in total cellular osmolarity during exercise with subsequent retention of sodium and water and eventual increase in edema.

Summary. Plasma sodium and potassium concentrations were determined in 71 cases of congestive failure uncomplicated by renal disease or by vomiting or diarrhea. Samples were drawn soon after admission and before any mercurial therapy in 56 of the patients and were obtained after the administration of these agents in 15 cases.

The mean values of 149.0 ± 7.2 mEq./L. for sodium and 4.8 ± 0.7 mEq./L. for potassium in the 71 cases of congestive failure were definitely higher than the normal means of 142.0 ± 3.1 mEq./L. and 4.06 ± 0.3 mEq./L. for the respective cations in a series of 73 control subjects. Sodium and potassium concentrations were slightly higher in severe than in moderate to mild congestive failure, but were not influenced by the type of heart failure, as shown by the lack of significant differences in the mean values for cases of predominant systemic engorgement and edema, cases with isolated pulmonary edema, and cases with combined left and right heart failure. Plasma sodium and potassium levels could not be correlated with blood urea nitrogen, indicating that abnormalities in electrolyte concentrations are independent of the azotemia that frequently accompanies congestive failure. The mean value for sodium was distinctly lower in the 15 patients who had received mercurial diuretics than in the 56 untreated patients, but no significant differences were found in the potassium concentrations of the 2 groups.

Hypernatremia, as indicated by a concentration exceeding the normal mean by more than twice its standard deviation, was found in 34 of the 56 untreated patients, whereas hyponatremia, comprising a comparable deviation below the normal mean, was found in 2 patients who had received no mercurial diuretics.

Serial determinations were made during recompensation in 26 cases and showed a slight fall in plasma potassium, but a more marked change in sodium. In 20 patients with an initially high sodium level averaging 152.8 mEq./L., there was a significant fall to a mean of 143.9 mEq./L. whereas in the other 6 patients, with an initially normal level, there was a slight rise that kept within the normal range.

The course of the plasma sodium concentration and body weight was

followed during recovery from cardiac decompensation in 6 patients and during a subsequent attempt at induction of congestive failure by sodium chloride supplements with or without ambulation in 4 of these patients. An essentially parallel fall in plasma sodium level and body weight during recovery was observed in 3 patients, and maintenance of plasma sodium at an abnormally high plateau until all edema had been evacuated was observed in the other 3 patients. The attempt at induction of congestive failure in 1 patient led to a marked rise in plasma sodium concentration with only a slight weight gain, strongly suggestive of initial retention of sodium; in the other 3 patients, it resulted in a rise in plasma sodium level and a more parallel weight gain, consistent with initial retention of sodium, but also explainable by primary water retention, accompanied by cellular uptake of water and release of sodium.

The relatively frequent finding of hypernatremia and relatively uncommon finding of hyponatremia in untreated congestive failure and the tendency for plasma sodium concentration to fall during recovery and to rise during induced decompensation are discussed in reference to the pathogenesis of congestive heart failure.

REFERENCES

1. **Bercu, B. A., Rokaw, S. N., and Massie, E.:** J. Lab. & Clin. Med., **34,** 1585, 1949.
2. **Briggs, A. P., Fowell, D. M., Hamilton, W. F., Remington, J. W., Wheeler, N. C., and Winslow, J. A.:** J. Clin. Invest., **27,** 810, 1948.
3. **Citron, D., Bercu, B., Lemmer, R., and Massie, E.:** Ann. Int. Med., **34,** 872, 1951.
4. **Darrow, D. C.:** J. Pediat., **28,** 515, 1946.
5. **Deming, Q. B., and Luetscher, J. A., Jr.:** Proc. Soc. Exper. Biol., & Med., **73,** 171, 1950.
6. **Edelman, I. S., Zweifach, B. W., Escher, D. J. W., Grossman, J., Mokotoff, R., Weston, R. E., Leiter, L., and Shorr, E.:** J. Clin. Invest., **29,** 925, 1950.
7. **Elkinton, J. R., and Squires, R. D.:** Circulation, **4,** 679, 1951.
8. **Farber, S. J., Alexander, J. D., and Eichna, L. W.:** J. Clin. Invest., **30,** 638, 1951.
9. **Fox, C. J., Friedberg, C. K., and White, A. G.:** Am. J. Med., **6,** 511, 1949.
10. **Iseri, L. T., Boyle, A. J., and Myers, G. B.:** Am. Heart J., **40,** 706, 1950.
11. **Kattus, A. A., Sinclair Smith, B., Genest, J., and Newman, E. V.:** Bull. Johns Hopkins Hosp., **84,** 344, 1949.
12. **Miller, G. E.:** Circulation, **4,** 270, 1951.
13. **Mokotoff, R., Ross, G., and Leiter, L.:** J. Clin. Invest., **27,** 1, 1948.
14. **Mosher, R. E., Boyle, A. J., Bird, E. J., Jacobson, S. D., Batchelor, T. M., Iseri, L. T., and Myers, G. B.:** Am. J. Clin. Path., **19,** 461, 1949.
15. **Oliver, B. B., Eisenberg, S., Lombardo, T., and Viar, W.:** J. Clin. Invest., **29,** 837, 1950.
16. **Parrish, A. E.:** J. Clin. Invest., **28,** 45, 1949.
17. **Peters, J. P.:** New England J. Med., **239,** 353, 1948.
18. **Sinclair Smith, B., Kattus, A. A., Genest, J., and Newman, E. V.:** Bull. Johns Hopkins Hosp., **84,** 369, 1949.
19. **Smith, R. G., Craig, P., Bird, E. J., Boyle, A. J., Iseri, L. T., Jacobson, S. D., and Myers, G. B.:** Am. J. Clin. Path., **20,** 263, 1950.
20. **Squires, R. D., Singer, R. B., Moffitt, G. R., Jr., and Elkinton, J. R.:** Circulation, **4,** 697, 1951.
21. **Squires, R. D., Crosley, A. P., and Elkinton, J. R.:** Circulation, **4,** 868, 1951.
22. **Warren, J. V., and Stead, E. A.:** Arch. Int. Med., **73,** 138, 1944.

CARDIORESPIRATORY RESPONSES AND ELECTROCARDIOGRAPHIC CHANGES DURING EXERCISE BEFORE AND AFTER INTRAVENOUS DIGOXIN IN NORMAL SUBJECTS*

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IN 1941 Liebow and Feil[9] reported the effects of digitalis upon the electrocardiogram after exercise in normal subjects. They found that prolonged digitalization of certain normal subjects produced changes in the ST segment and T wave resembling those of spontaneous or induced angina pectoris. They suggested that a check should be made concerning digitalis administration whenever the exercise test is performed.

The exercise test has become increasingly popular as an aid in making the diagnosis of coronary insufficiency. Furthermore, the digitalis glycosides are commonly used in the treatment of patients with heart disease. Therefore, studies are needed to show the effects of the digitalis glycosides during and following exercise in man. The present report summarizes some cardiorespiratory observations and electrocardiographic changes during and after exercise on 20 normal subjects following intravenous digoxin. Similar observations are being made in patients with heart disease and the results will be reported in a subsequent communication[14].

Material and Method. Observations were made on 20 normal subjects (19 males and 1 female) ranging in age from 20 to 52 years. Most of them were physicians or medical students. The resting blood pressure and electrocardiogram were normal in each subject. None of the subjects had taken a digitalis preparation at any previous time.

The performance of the exercise test and the respiratory and ventilatory measurements were essentially similar to those described in previous studies[4,5,16]. The exercise tests were performed under non-basal conditions, and the subjects were breathing room air through a face mask. The speed and grade of the

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TABLE 1. THE AVERAGE VALUE OF CERTAIN CARDIORESPIRATORY DETERMINANTS DURING THE EXERCISE TEST BEFORE AND AFTER DIGOXIN IN TWENTY NORMAL SUBJECTS

	Before Digoxin			After Digoxin			
	Rest	Exercise	Recovery	Rest	Exercise	Recovery	S. E. *
Ventilation ($L/M^2/min.$)	3.50	9.35	4.45	3.05	8.90	4.40	0.14
Respiratory efficiency (vol.%)	4.1	5.4	4.0	4.4	5.4	4.0	0.85
Oxygen Consumption ($cc./M^2/min.$)	142	499	193	131	476	199	6.48
Oxygen Transport ($cc./M^2/min.$)	1.69	4.39	2.14	1.85	4.54	2.28	0.09
Blood pressure (mm. Hg)	129/79	145/88	133/82	131/80	145/80	136/82	2.40/1.48
Oxygen Debt (%)			10.5			11	0.79

* S. E. = Standard error of the mean difference.

treadmill ergometer were fixed at 1.73 and 10%, respectively.

A CB lead was used[16,17] for recording the electrocardiogram. The heart rate was obtained by means of an electronic counter which is activated by the QRS complex. The cycle length and the QT interval were measured in at least 2 consecutive complexes in each tracing. The TQ interval is the difference between the corresponding cycle length and the QT interval. The QT interval corrected for heart rate (QTc) is derived from the modified Bazett's formula[13]. The amplitude of 3 or more consecutive T waves was measured in lead CB_4 or CB_5. The average amplitude of an equal number of high and low T waves was recorded whenever marked respiratory variation in the complexes occurred.

All the data have been treated statistically for comparison.

Results. The average value of certain cardiorespiratory determinants during rest, exercise and recovery, before and after digoxin are presented in Table 1. No statistically significant difference was found in ventilation, respiratory efficiency, oxygen consumption, or blood pressure in any of the 3 periods of the test. The oxygen transport increased slightly after digoxin in most subjects, but the difference is not significant in such a small series of observations. There was no change in the mean value of the oxygen debt.

TABLE 2. THE AVERAGE HEART RATE, QT/TQ, QTc INTERVAL AND AMPLITUDE OF THE T WAVES DURING THE EXERCISE TEST BEFORE AND AFTER DIGOXIN

	Before Digoxin			After Digoxin			
	Rest	Exercise	Recovery	Rest	Exercise	Recovery	S. E.***
Heart Rate/min.	80**	115*	88*	64	107	78	2.42
QT_C	.41	.43	.40	.40	.42	.40	0.005
QT/TQ	.92*	1.44	.95	.74	1.32	.84	0.48
T Wave (mm.)	4.5	3.2**	4.2*	3.5	1.6	2.9	0.35

* The differences before and after digoxin are significant at the 5% level using "Student" t-test.
** The differences before and after digoxin are significant at the 1% level using "Student" t-test.
*** S. E. = Standard error of the mean difference.

The test is divided into 3 periods: a.) resting, 5 minutes; b.) exercise, 10 minutes; c.) recovery, 10 minutes. Simultaneous and continuous recording of various circulatory and respiratory determinants and the chest electrocardiogram were made minute by minute throughout the test.

Each subject performed an exercise test before receiving intravenous digoxin. Approximately 15 minutes following the control test. 0.9–1.5 mg. of digoxin (0.15 mg. per 10 kg. of body weight), diluted to 20 to 30 cc. with physiologic saline, was injected intravenously over a period of 5 minutes. The exercise test was repeated under identical conditions approximately 1 hour and 30 minutes after the digoxin administration. The exploring and indifferent electrodes were placed in the positions they occupied during the control exercise test.

The entire procedure was repeated without digoxin on other days in 5 of these subjects.

The average heart rate, QT/TQ, QTc interval and amplitude of the T waves before, during, and after exercise are summarized in Table 2.

The heart rate was slower in 18 of the 20 subjects in the 3 periods of the exercise test after the digoxin administration and it remained unchanged in the remaining 2 subjects. There is a significant difference between the mean heart rate before and after digoxin for the whole group. Although the mean QT/TQ is slightly lower after digoxin, the difference is not significant except at rest. There is no significant difference between the mean QTc interval before and after digoxin in any of the 3 periods of the

exercise test. The mean amplitude of the T wave was lower in 17 subjects and unchanged in 3 after digoxin. There is a significant difference between mean values during exercise and recovery before and after digoxin.

No significant changes in the ST segment were observed in any subject during the 3 periods of the exercise test before digoxin and during the period of rest after digoxin. There was no deviation of the ST segment in the exercise electrocardiogram after digoxin in 15 of the 20 subjects. Figure 1 shows 2 such sets of exercise electrocardiograms in a normal subject before and after digoxin. Five subjects showed ST depression of more than 1 mm. during exercise and early recovery after digoxin (Figures 2 and 3). Each had a normal electrocardiogram throughout the control exercise test before digoxin was injected. The T waves became diphasic or slightly inverted in 3 and very low in the remaining 2 subjects. One of these 5 subjects showed 2 ventricular premature beats in bigeminy immediately after exercise (Figure 4). Diphasic or flat T waves during exercise and early recovery occurred in 2 other normal subjects. These 7 subjects do not differ significantly from the remaining 13 in any of the cardiorespiratory determi-

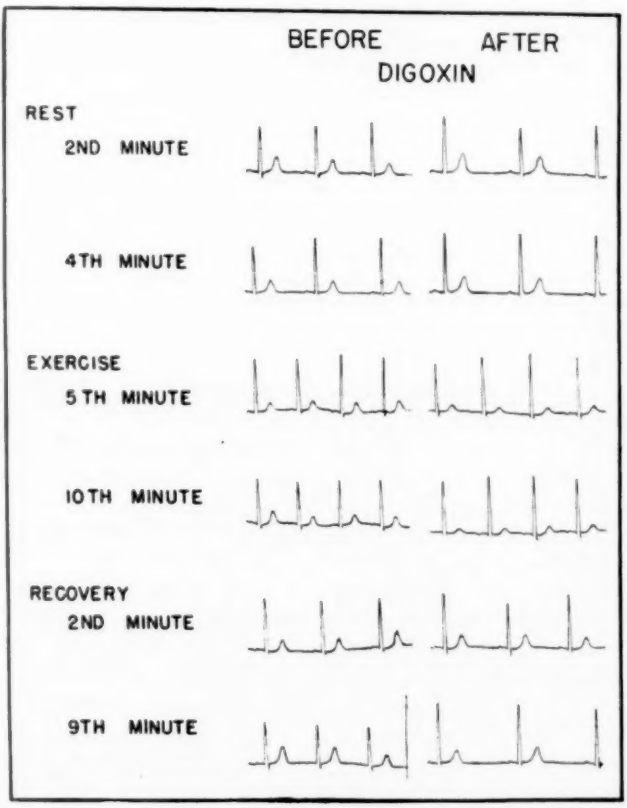

FIG. 1. Exercise electrocardiogram before and after digoxin in a normal subject who showed no abnormalities in the tracings throughout the test.

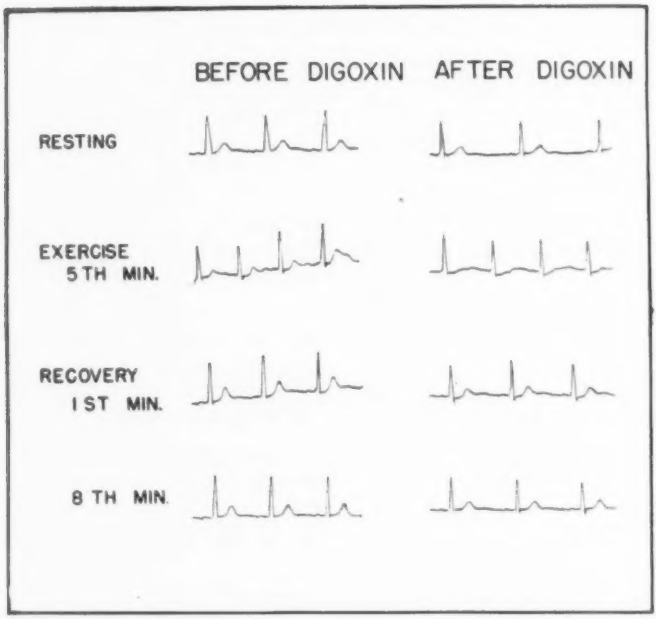

FIG. 2. The subject showed a normal electrocardiographic response in the exercise test before digoxin. Note the diphasic T wave during exercise and the depressed ST segment during exercise and early recovery after digoxin.

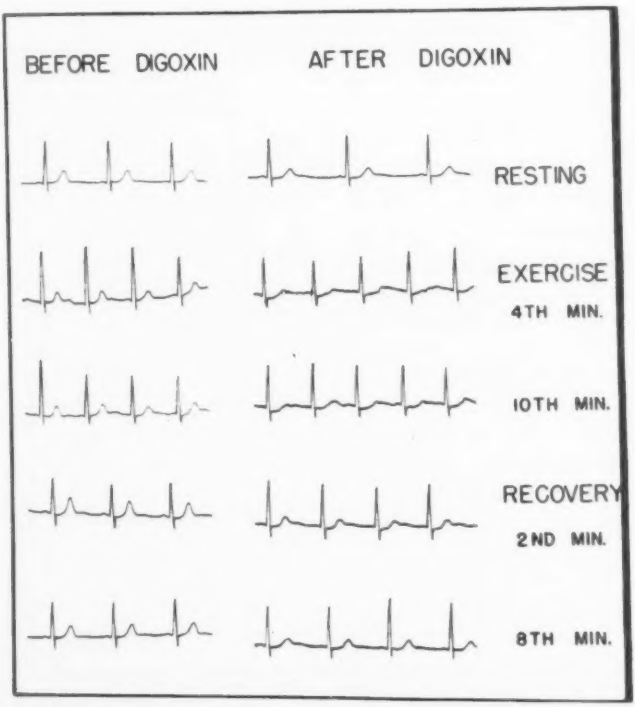

FIG. 3. This subject showed the same changes as those described in Fig. 2.

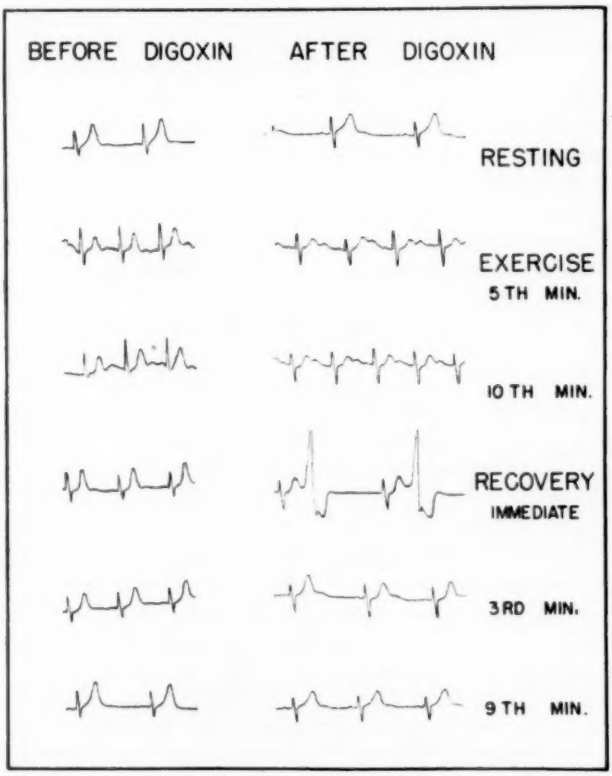

FIG. 4. The electrocardiographic changes during and after exercise in this subject were essentially normal before digoxin. Following digoxin administration the ST segment was depressed during exercise and 2 ventricular premature beats in bigeminy were recorded immediately after exercise. Note that the U wave became more distinct during exercise after than before digoxin.

nants during exercise. Abnormalities of the ST segment and the T wave returned to normal in each instance after the 6th minute of recovery.

We did not encounter significant changes in the PR interval or the QRS complex. No subject showed a high T wave during exercise.

Exercise tests were performed on 5 of these normal subjects before and after a resting period of approximately 1 hour and 30 minutes. Digoxin was not administered in this group. There were no significant changes in the cardiorespiratory determinants or in the electrocardiogram.

Discussion. A therapeutic dose of intravenous digoxin produced slowing of the heart rate and reduction of the height of the T wave during the exercise test. Our observations confirm the reports of Liebow and Feil[9] that abnormal changes in the exercise electrocardiogram may develop in a certain proportion of normal subjects who have received a therapeutic dose of a digitalis preparation. Distinct electrocardiographic abnormalities during and after exercise were observed in 7 of the 20 subjects studied within 2 hours after completion of the injection. These abnormalities are most marked during exercise and simulate those observed

in patients with coronary insufficiency after they have performed the standard exercise test.

Electrocardiographic changes in man following prolonged digitalis administration have been described in detail by many investigators[8,10]. Sanberg, *et al.*[12] using esophageal leads have studied these electrocardiographic changes and demonstrated that the action of digitalis on the human heart is predominantly in the subendocardial myocardium.

It has been shown by the technique of coronary sinus catheterization[1,2] that digitalis glycosides given to normal subjects over a period of 1 to 2 hours may reduce the efficiency of the myocardium. It is possible that the myocardial function may be even more impaired during exercise in some normal individuals who have been digitalized.

The problem probably will be nearer solution as studies of the energy metabolism of heart muscle yield more information[3,11]. It is likely that the administration of digitalis glycosides actually interferes with myocardial metabolism (during exercise) in normal subjects. Liebow and Fiel[9] suggested that abnormalities in the exercise electrocardiogram of normal subjects who have been digitalized may be due to inadequate oxygen supply to the myocardium. Our results indicate that the 7 subjects with electrocardiographic abnormalities showed no significant difference in oxygen consumption during exercise or recovery before and after digoxin. It is not certain whether the electrocardiographic abnormalities indicate myocardial ischemia as postulated by Liebow and Fiel or whether they reflect an undefined effect of digitalis preparations on oxygen extraction and utilization by the myocardium.

Recent studies of hemodynamic effects of digoxin in patients with and without heart failure by Harvey and associates from Cournand's laboratoy[5,6,7] have clearly demonstrated that the reaction of patients with failing hearts to acute digitalization is distinctly different from that observed in patients with normal or compensated hearts. Following acute digitalization patients with heart failure usually showed a decrease in the right ventricular and pulmonary artery pressures and a definite increase in the cardiac output. On the other hand, digoxin had no effect on the right ventricular and pulmonary artery pressures in the absence of heart failure or in normal subjects. In these cases the cardiac output decreased or remained unchanged. Furthermore, Bing *et al.*[2] have shown that the efficiency of the heart in patients with cardiac failure is definitely greater after digitalization. It has been assumed that digitalis glycosides actually improve energy liberation and mechanical contraction of the failing myocardium[3].

Our preliminary observations of cardiorespiratory responses and electrocardiographic changes before and after digoxin in several patients with heart failure suggest that their response is different from that of normal subjects. A larger number of cases must be studied, however, before conclusions can be drawn.

Summary and Conclusion. 1. This report summarizes some of the cardiorespiratory effects and the electrocardiographic changes during exercise performance before and within 2 hours after intravenous digoxin injection in 20 normal subjects.

2. There is no statistically significant difference during the exercise test before and after digoxin in any of the following determinants: ventilation,

respiratory efficiency, oxygen transport, blood pressure, and oxygen debt.

3. The heart rate is slower and the amplitude of the T waves lower after than before digoxin. There is no significant difference in the QT/TQ or the QTc interval.

4. In contrast to the control exercise test, definite electrocardiographic abnormalities during and after exercise occurred after digoxin in 7 of the 20 subjects. These changes simulated those of coronary insufficiency, namely, ST depression, diphasic or flat T waves, and occasional ventricular premature beats.

5. The mechanism of the production of the electrocardiographic abnormalities is not established. The possibility of a disturbance in the energy metabolism of the myocardium including oxygen extraction and utilization following digoxin administration and exertion has been mentioned.

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REFERENCES

1. **Bing, R. J., Hammond, M. M., Handelsman, J. C., Powers, S. R., Spencer, F. C., Eckenhoff, J. E., Goodale, W. T., Hafkenschiel, J. H.,** and **Kety, S. S.**: Am. Heart J., **38**, 1, 1949.

2. **Bing, R. J.,** and **Daley, R.**: Am. J. Med., **10**, 711, 1951.

3. **Biorck, G.**: Scandinav. J. Clin. & Lab. Invest., **2**, 242, 1950.

4. **Bruce, R. A., Lovejoy, F. W., Jr., Pearson, R., Yu, P. N. G., Brothers, G. B.,** and **Velasquez, T.**: J. Clin. Investigation, **28**, 1423, 1949.

5. **Ferrer, M. I., Harvey, R. M., Cathcart, R. T., Webster, C. A., Richards, D. W., Jr.,** and **Cournand, A.**: Circulation, **1**, 161, 1950.

6. **Harvey, R. M., Ferrer, M. I., Cathcart, R. T., Richards, D. W., Jr.,** and **Cournand, A.**: Am. J. Med., **7**, 439, 1949.

7. **Harvey, R. M., Ferrer, M. I., Cathcart, R. I.,** and **Alexander, J. K.**: Circulation, **4**, 366, 1951.

8. **Larsen, R., Neukirch, F.,** and **Nielson, N. A.**: Am. Heart J., **13**, 163, 1937.

9. **Liebow, I. M.,** and **Feil, H.**: Am. Heart J., **22**, 689, 1941.

10. (a) **McMillan, T. M.,** and **Bellet, S.**: The effects of digitalis on the electrocardiogram. Cyclopedia of Medicine, **3**, 465, Philadelphia, F. A. Davis Co., 1932. (b) **McMillan, T. M.,** and **Bellet, S.**: Effect of digitalis on the electrocardiogram. In Stroud's Diagnosis and Treatment of Cardiovascular Disease, **1**, 636, Philadelphia, F. A. Davis Co., 1950.

11. **Olson, R. E.,** and **Schwartz, W. B.**: Medicine, **30**, 21, 1951.

12. **Sandberg, A. A., Scherlis, L., Grishman, A.,** and **Wener, J.**: Circulation, **2**, 921, 1950.

13. **Taran, L. M.,** and **Szilagyi, N.**: Am. Heart J., **33**, 14, 1947.

14. To be reported.

15. **Yu, P. N. G., Bruce, R. A., Lovejoy, F. W., Jr., McDowell, M. E.**: Circulation, **3**, 368, 1951.

16. **Yu, P. N. G., Bruce, R. A., Lovejoy, F. W., Jr.,** and **Pearson, R.**: J. Clin. Investigation, 29, 279, 1950.

17. **Yu, P. N. G.,** and **Soffer, A.**: Studies of electrocardiographic changes during exercise (Modified double two-step test), Circulation, in press.

LEUKEMIA AND OTHER MALIGNANCIES IN PHYSICIANS

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Leukemia is said to occur about 8 to 9 times as often as a cause of death in radiologists as in other physicians[2,3,4,6,7]. The ratio of this disease is also high in dermatologists. This excess in leukemia has been associated with strong exposure to radiation energy.

Several questions now arise: 1) Are the consequences of exposure limited to the 2 groups of specialists, that is, to less than 1.5% of the medical profession, or do they extend also to general practitioners and internists? 2) How rapidly does exposure to Roentgen-rays and radium augment the incidence of leukemia? 3) What repercussions does this exposure have in systems other than the hemopoietic? 4) Do the effects of radiation energy in the medical profession differ from those in other professions, and, if so, how to explain the diversity with regard to the duration of the latency period and the primarily affected organ? and 5) what measures should be taken to diminish the danger of leukemia in physicians?

To answer these questions, we analyzed the causes of deaths of all physicians whose necrologies appeared in the Journal of the American Medical Association during five years, between January 1, 1947 and December 31, 1951.* For comparison we used the official annual report on deaths in the United States, 1948[11]. In the 5 years, 1947 to '51, a total of 14,516 physicians were reported dead, but the cause of death was disclosed in only 11,481 cases (79.2%). In our calculations we shall disregard the other 3,035 deaths which are scattered throughout the whole age scale,† and we will limit ourselves to the 11,481 physicians of Table 1.

TABLE 1.

Deaths of physicians, 1947-1951, with known cause of deaths

Age in years	all	leukemia	other malignancies
-29	95	7	7
30-34	127	4	11
35-39	199	5	17
40-44	440	10	36
45-54	1,084	12	130
55-64	2,182	26	261
65-74	3,803	43	517
75-84	2,896	21	384
85-. .	755	4	63
all	11,481	133	1,426

* In a note to the correspondence column of the Journal of The American Medical Association, we[10] gave some preliminary results.

† According to the age groups of Table 1: 29, 49, 67, 84, 281, 514, 909, 785, and 317, respectively.

Leukemia appears as a cause of death 133 times (1.2%), and all other malignancies 1,426 times (12.4%), making a total of 13.5% of all 11,481 deaths. Leukemia is found in every age group, from the youngest to the oldest. Of all fatal malignancies among physicians, 8.5% are leukemias as compared with 3.5% in white males.

In physicians, the ratio of leukemia to all malignancies diminishes with rising age. In the order of the age groups of Table 1, the ratios are 50.0± 13.3, 26.7, 26.1, 21.8, 8.5, 9.1, 7.7, 5.2, and 6.0%, as compared with 18.6, 13.3, 9.9, 5.7, 4.4, 3.7, 3.0, 2.4, and 1.3 in white males of the general population. In all age groups the ratio of leukemia to all malignancies is 2 to 3 times higher in physicians than in the white male population. In the youngest group (25 to 29 years), the ratio is equal to that encountered in children of pre-school age.* In 30 to 34-, 35 to 39-, and 40 to 44-year old physicians, leukemia ratios are increased to a level characteristic of the age of 15 to 24 years. Of those physicians who succumbed to a malignancy during the first 15 years of professional work, that is at the age of 25 to 39 years, 32.7± 6.5% died of leukemia, as compared with 12.8±0.6 for all white male cancer victims; the difference is statistically significant.

In physicians, the proportion of leukemia to all 11,481 deaths is 1.2±0.1%, while in all white males over 25 it is 0.52±0.01%. For the single age groups, from the youngest (25 to 29) to the highest (85+), the ratios of leukemia to all deaths are much higher in physicians than in all white males (Table 2).

The situation regarding non-leukemic cancers is entirely different. The ratios of cancer, exclusive of leukemia, to all deaths are low in physicians who died within the ages of 35 to 74 years. For the 40 to 74-year old physicians the ratio of non-leukemic cancers was 12.6±0.4%, and for all white males of corresponding age 15.6±0.05%. In the age groups 25-34 the ratios of non-leukemic cancer to all deaths are slightly higher than in white males.

Calculating for each age group the proportion of *all* malignancies, inclusive of leukemia, to all deaths, we find an interesting pattern. At the beginning of the age scale the ratio for physicians is more than twice that for

TABLE 2.

Percentage of leukemia of all deaths in (a) Physicians and (b) all white males

Age at death	Physicians %	All white males %
25-	7.3	1.3
30-	3.1	1.1
35-	3.4	0.9
40-	2.3	0.75
45-	1.1	0.65
55-	1.2	0.63
65-	1.1	0.50
75-	0.8	0.32
85-	0.6	0.10
crude ratio for all age groups.	1.2	0.52

* In all white males, in 1948, the percentages of leukemia dropped from 54 in infancy, to 46, 47, 43, 35, and to 22% at the age of 20 to 24.

all white males (14.7 versus 6.9%), but the difference is statistically insignificant. This excess diminishes gradually in the 30's, vanishes around the age of 40, and turns into the opposite direction, that is, into a substantial deficit in each of the 4 age groups between 40 and 74 years, with the largest deficit at 55 to 64 years (13.2±0.7 versus 17.3±0.1%). After the age of 75, physicians have slightly higher malignancy ratios than white males. Whether the excess in the aged physicians is true, or due to faulty recording in the general population, can not be stated (Table 3).

mortality of all white males was in 1948 (2,019 versus 1,654 per 100,000). However, two-thirds of that difference are accounted for by the age distribution. Given the age structure of physicians of 1940, white males (1948) would have a standardized mortality of 1,870 per 100,000, and the difference in disfavor of physicians thus shrinks from 368 to 149 per 100,000. Because of the diminished mortality in the 1940's the difference is even smaller than that, probably around 100, that is, about 5% of total mortality. Such a difference may be completely ignored when ratios of leukemia and other can-

TABLE 3.

Percentage of non-leukemic cancers and of all cancers to all deaths in Physicians and in all white males

Age at death	All non-leukemic cancers		All malignancies	
	Physicians %	All white males %	Physicians %	All white males %
25-	7.4	5.6	14.7	6.9
30-	8.7	7.4	11.8	8.5
35-	8.1	8.4	11.5	9.3
40-	8.2	12.4	10.5	13.1
45-	12.0	13.9	13.1	14.6
55-	12.0	16.7	13.2	17.3
65-	13.6	16.0	14.7	16.5
75-	13.2	13.1	14.0	13.4
85-	8.3	8.1	8.9	8.2
crude ratio for all age groups.	12.4	14.1	13.5	14.6

Provided the total mortality of physicians deviates but little from that of all white males, the low ratios of cancer in physicians who died at 40 to 74 indicate low cancer mortality rates. Not knowing the total number nor the age distribution of the profession in 1947 to 1951, we sought orientation in Dublin and Spiegelman's[2] paper (1948) covering the American physicians of 1938 to 1942 for the age of 35 to 74 years. In these years the crude total mortality of 35 to 74-year old physicians was much higher than the corresponding crude cers are used for the estimate of rates.

In the age group 35 to 74, of all physicians with known cause of death in 1947 to 1951, 1.26% died of leukemia, and 12.46% from all other cancers. Hence, leukemia mortality amounted roughly to 2,019 x 1.26 / 100 = 25.4± 4.0 per 100,000, and mortality from all other malignancies to 252.4 per 100,000, giving a total cancer mortality of 277.8 per 100,000 physicians of 35 to 74 years of age. The corresponding age adjusted rates for all white males in 1948 were: 10.9±0.2 + 285.9 = 296.8 per 100,000. The almost 2.5 times in-

creased mortality from leukemia in physicians of the 35 to 74 age group does not show up in the total cancer mortality which is even (though insignificantly) below that of all white males.

The 12% deficit in the sum total of non-leukemic malignancies is of interest. Unfortunately, in 268 of the 1,426 deaths from malignancy (1947 to 1951) the organ of tumor origin is not stated. It cannot be said, therefore, to what degree each of the organs participated in the deficit of the non-leukemic cancers.

In 1948, in white males 35 to 74 years of age, 0.6% of all deaths were due to leukemia; in the total of physicians (1947 to 1951) the corresponding value was 1.259, and in the sector of radiologists plus dermatologists (1938 to 1942), according to Dublin and Spiegelman[2], 4.5%. Since among 100 physicians who died at the age of 35 to 74 years, 1.25 were radiologists or dermatologists, 4.5 x 1.25 / 100 = 0.056 gives the number of leukemias in these two specialties per 100 dead physicians. Subtracting 0.056 from 1.259, which is the figure for leukemia fatalities among 100 physicians who died at 35 to 74 years of age, we get 1.203 ± 0.031 leukemias per 100 physicians who were neither radiologists nor dermatologists. The value 1.2 implies that the leukemia risk of all 35 to 79-year old physicians outside of these two specialties is twice normal.

Not all physicians work fluoroscopically or roentgenologically. The leukemia risk of those who do work is therefore much more than about twice normal. Furthermore, during the last 10 years the Roentgen-ray risk per 100 radiologists hardly increased; it rather diminished or remained stable, while the Roentgen-ray risk per 100 general practitioners and diagnosticians increased. A higher percentage of physicians was using fluoroscopy in 1947 to 1951 than in 1938 to 1942. The difference in the leukemia risk as found between radiologists and non-radiologists in former surveys is therefore diminishing.

Comment. In physicians Roentgen-ray and radium cause leukemia and epitheliomas. Dial painters and radium miners suffered other effects. In these 2 groups, radium failed to produce leukemias or epitheliomas. The painters had a tremendously increased frequency of bone sarcomas and the miners a 25 to 29 times increased incidence of lung cancers.

As was said above, physicians have an excess mortality from leukemia in all age groups, including that of 25 to 29 years. Evidently, the minimum latency period of induced leukemias is but a few years. This seems surprising, as the first paper on this subject, by von Jagic, Schwarz and von Siebenrock[5], was published not earlier than 1911. Most probably at that time the number of exposed was too small, and even if single cases occurred earlier, they were not recognized. Also, the first mutilating skin epitheliomas of the roentgenologists had a short latency period (the first report was published in 1902), but as a rule it was longer.

In radium induced bone sarcomas of the dial painters in New Jersey, the first recognized case died 6½ years following initial exposure*. But the average and maximum latency period of the radium-induced bone malignancies is much longer. The 41st victim of this disease, engaged in dial painting in 1917, died not earlier than in 1951. Up to that time, of the approximately 800 persons engaged in dial painting in New Jersey, not more than 30 per-

* The first 5 fatalities, unrecognized as to etiology, occurred 4 to 5 years after exposure. The persons died of bone necrosis and severe anemia.

sons should have died of cancer of all forms, including leukemia.

Radon- and radium-induced lung cancers in the mine workers of Joachimsthal (and probably also in Schneeberg) have a minimum latency period of not less than 15 to 17 years, with a range up to about 40 years. Obviously, the duration of latency in radiation-induced malignancies depends on the intensity of exposure, on the route taken by the rays or radioactive substance, the speed with which the latter are eliminated, the degree of the individual's cancer disposition, and the ability of the respective tissue to grow and multiply.

In physicians working roentgenoscopically, the Roentgen-rays hit the unprotected flat bones of the upper part of the sternum, ribs, clavicles, spine, jaw and skull, penetrating the thin compacta and inducing neoplastic growth in the hemopoietic centers of the spongiosa. If Roentgen-ray exposure is frequent, the invisible damage quickly accumulates and, depending on the degree of the individual's general cancer disposition, leads more or less rapidly to leukemia. On the way to and through the bones the Roentgen-rays also hit many other tissues and organs, but the latter apparently do not show any excess in cancer incidence; they participate in the cancer deficit.

In dial painters, the radium salt remained in the anterior part of the mouth until it was swallowed. Small parts of the radium salt probably were never removed from the sub- and perilingual region of the mouth mucosa and therefore caused local inflammation of the soft tissues, osteitis and bone necrosis. Most of the radium salt, however, was swallowed and passed the digestive wall somewhere to be transported by the blood and deposited as radium phosphate in the bones, predominantly in the compacta.* The radius of the alpha particles is small, and also that of the beta rays may not be much larger, because of the shielding action of the bone calcium. Thus the radium acted only in the close vicinity of the deposits. The amount of radium in the compacta was so much larger than in that part of the spongiosa which in adults contains red marrow, that many bone sarcomas but no leukemias were created. Between 15 and 24% of the ingested radium was transported to other organs, but remained there too short a time to do them harm. The pertinent question is, whether and why there was a cancer deficit in these organs.

In radium miners a large part of the inhaled substance is daily exhaled. The response therefore is slow and the final outcome after a long latency period is a 25 to 29 times increased frequency of bronchogenic carcinoma. Neither in the bone compacta nor in the spongiosa was there enough radioactive substance to interfere with the late development of lung malignancies. However, in radium miners lung cancers interfered with the development of cancers in all other organs, causing a substantial deficit in primary tumors of these organs. This deficit is exemplifying the rule of inverse association (Peller[8,9]).

The comparison of the 3 groups of people exposed to Roentgen-rays or radium shows that the site of the radiation-induced primary neoplasm and its histological and clinical characteristics are not determined by disposition, but by 1) the route taken by the carcinogenic agent, 2) the penetrating power and action radius of the rays and 3) the chemical composition of the natural or artificial radio-

* From 10 to 180 micrograms, or 66 to 85% of the whole daily ingested radium, were deposited in the bones.

active substances: pure or a compound.

We believe that it is the popularization of the fluoroscopic examination which accounts for the increase in leukemia ratios from 0.51% (March[6,7]), 0.53% (Henshaw and Hawkins[4]), and 0.65% (Dublin and Spiegelman[2,3]) to 1.20% in our survey. In the near future the ratio of leukemia is likely to rise still more among general practitioners and diagnosticians, unless proper protective measure will be devised. The protection afforded by the common use of apron and gloves is not satisfactory. New designs, such as the lead-glass-fabric gown described by Archer *et al.*[1] may diminish the danger of Roentgen-rays to arms and legs, but this is not decisive, as such a gown leaves unprotected the upper parts of the thorax, neck and head, which, in our opinion, are the first line of attack that leads to the excess of leukemia in physicians. Therefore an additional protective hood is necessary.

Summary and Conclusions. 1) Physicians have an increased and further increasing risk of developing leukemia. This risk is not limited to radiologists and dermatologists, but is shared by the large body of physicians many of whom routinely use fluoroscopy.

2) The increased mortality from leukemia is already apparent in the age group 25 to 29 years, and is about three times normal in all age groups.

3) In physicians almost 9% of all fatal malignancies appear as leukemia.

4) In the age group 25 to 34, physicians also have an increased mortality from cancers other than leukemia, whereas the risk of dying from non-leukemic malignancies in the group 40 to 74 is diminished.

5) The minimum latency period of Roentgen-ray and radium cancers, whether leukemia or other malignancies, is shorter than 5 years of exposure; when radium or radon enters the body by inhalation, the minimum latency is 4 to 5 times as long, but the excess incidence of cancer in the organ of main deposition, the lung, is nevertheless tremendous.

6) As in other examples of additional exposure, it is the carcino-relevant agent in question and the route by which it enters the body which determine the spot of origin of the additional tumors, influence the time of their appearance and change the distribution of cancers by site in the whole sample, not only by augmenting the number of tumors of a certain organ, but also by creating indirectly a tumor deficit in organs not affected by the agent in question. The organ of tumor manifestation is independent of any hypothetic organ disposition. The duration of the latency period is influenced by the degree of the bodily cancer disposition, by the growth potentialities of the exposed organ or tissue and by the concentration of the carcinogenic agent.

REFERENCES

1. **Archer, V. W., Cooper, G., Jr., Kroll, J. G.,** and **Cunningham, D. A.**: J. Am. Med. Assn., **148**, 106, 1952.
2. **Dublin, L. I.,** and **Spiegelman, M.**: J. Am. Med. Assn., **137**, 1519, 1948.
3. **Dublin, L. I., Spiegelman, M.,** and **Leland, R. G.**: Postgraduate Medicine, **2**, 189, 1947.
4. **Henshaw, P. S.,** and **Hawkins, J. W.**: J. Nat. Cancer Inst., **4**, 339, 1944.
5. **von Jagic, N., Schwarz, G.,** and **von Siebenrock, L.**: Berlin klin. Wchnschr., **48**, 1220, 1911.
6. **March, H. C.**: Radiology, **43**, 275, 1944.
7. Idem: Am. J. Med. Sci., **220**, 282, 1950.
8. **Peller, S.**: Arch. f. Gynäk., **118**, 59, 1923.
9. Idem: Human Biology, **11**, 130, 1939.
10. **Peller, S.,** and **Pick, P.**: J. Am. Med. Assn., **147**, 893, 1951.
11. Vital Statistics of the United States, 1948, Part I, Federal Security Agency, P. H. Service, Nat. Off. of Vital Statistics, Washington, D. C., 1950.

DERMATOMYOSITIS AND MALIGNANT NEOPLASM*

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SPECULATION concerning the etiologic factors involved in the production of the collagen diseases has covered many fields. The current popular theory concerns the state of hypersensitivity in which there is considered to be a specific reaction of mesenchymal tissue, particularly collagen material, to various antigenic or sensitizing agents[3,7,9,10]. Pagel[8] has pointed out the resemblance of the basic pathology of the collagen diseases and anaphylactic type of allergy. He suggests that the sensitizing agent may be a foreign or modified serum, an abnormal protein or a bacterial antigen. In a recent review of the literature, Brunner and Lobriaco[2] collected 17 cases and added 1 of their own of dermatomyositis associated with malignant neoplasms. They suggest that the antigenic stimulus might be provided by products of tumor growth or breakdown. The symptoms of dermatomyositis in 4 of these cases[1,2,4] improved with treatment of the neoplasm and recurred with exacerbation of the tumor.

The present report concerns 2 cases of dermatomyositis with malignancy in which the initial complaints were due to the dermatomyositis.

Case Reports. CASE 1. A 50-year old white male was first admitted to the hospital on February 23, 1949, complaining of hoarseness, difficulty in swallowing and an erythematous rash on his face, neck, scalp and hands. His symptoms began insidiously about January 1, 1949. He had no gastrointestinal symptoms.

Examination on his first admission revealed a well developed and well nourished white male. There was a mild erythematous scaling rash involving the head, neck and dorsum of the hands. The mouth and throat appeared normal. Direct laryngoscopy revealed moderate redness and edema of the arytenoids and some thickening and redness of the vocal cords. A biopsy of the right vocal cord revealed mild ulceration and thinning of the stratified squamous epithelium. The pathologic report stated, "the supporting tissue is comprised of dense collagenous connective tissue which is irregularly infiltrated with granulocytes, and there is also fibrous proliferation. The etiologic agent is not determined." Roentgenograms of the pharynx and esophagus revealed the valleculae to fill unusually well with barium and to retain it for some time. The esophagus appeared normal. It was felt that the patient's symptoms were part of a generalized vitamin deficiency, and accordingly he was discharged on March 7 on a high vitamin diet and was given supplemental multi-vitamin tablets.

He returned to his occupation as a mail carrier for 3 weeks but soon noted the onset of pain, soreness and weakness of the muscles of the shoulder girdle, arms and thighs. These symptoms rapidly increased in severity, and for the 3 weeks prior to his last hospitalization he was forced to remain in bed. He had no gastrointestinal symptoms other than dysphagia.

His last admission was on April 22, 1949, at which time examination revealed an acutely ill and uncomfortable white male. The erythematous rash was more severe, and there was periorbital edema. The blood pressure was 120/65, the pulse was 84, and the temperature was 99.4°F. The apical impulse was in the fifth interspace, 2.0 cm. left of the midclavicular line. The heart tones were of poor quality, and extrasystoles were noted. The abdomen was flat, but the liver was not felt and no masses were noted. Marked tenderness and weakness of the paraspinal and

* Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his own study and do not necessarily reflect the opinion or policy of the Veterans Administration

shoulder girdle muscles were present. The overlying skin was warm, firm and edematous. Deep tendon reflexes were present but diminished.

Laboratory studies were as follows: Serologic test for syphilis was negative. The erythrocyte count was 3,880,000, the hemoglobin 12.0 gm. The white blood cell count was 10,050 and the differential count revealed 67% polymorphonuclear neutrophils, 32% lymphocytes, and 1% eosinophils. The uncorrected sedimentation rate was 33.0 mm/hr. (Wintrobe). Urinalysis showed a specific gravity of 1.024; reduction was negative; there was a trace of albumin; and the microscopic study was negative. Roentgenograms of the chest were negative.

FIG. 1.—Case 1. Typical adenocarcinoma of the stomach, removed surgically. X20.

An electrocardiogram on May 10 was normal but on July 5 it revealed ventricular and nodal extrasystoles. His course was rapidly downhill. On May 23 a rounded, hard, epigastric mass was felt, and Roentgen-ray examination on May 31 again revealed barium to be retained in the valleculae. The esophagus appeared atonic and slightly dilated. A large filling defect was noted in the antral portion of the stomach, which was considered to be a large carcinoma. The erythrocyte count had fallen to 1,700,000 by May 31 and he was given repeated blood transfusions. On June 23 the erythrocyte count reached 5,410,000. Despite his extremely poor condition, it was felt that an exploratory laparotomy was justified. Accordingly, on June 28 this was done, and a large carcinoma of the stomach with extension into the gastrocolic ligament and adjacent transverse colon was found and resected. Microscopic examination of the tissue (Fig. 1) revealed a typical adenocarcinoma of the stomach. His immediate postoperative course was uneventful; however, on July 4 he choked and aspirated liquids during swallowing. His temperature rose to 102°F., and he developed cyanosis and marked dyspnea. Roentgenogram of the chest showed the left hemithorax to be completely and homogeneously opaque. Following repeated tracheal suction and oxygen his condition improved, and a chest film on July 6 revealed almost complete clearing of the lung fields. On July 8, after seeming to be much improved, he abruptly expired.

Necropsy was performed 5 hours after death. A crusting erythematous rash was present over the head, shoulders, chest, knees and dorsum of both hands. Subcutaneous fat was almost entirely absent. The entire musculature was pale and edematous. There was a perforation along the suture line of the gastroduodenostomy with a secondary peritonitis, and a small left subphrenic abscess was noted. The left upper, left lower and right lower lobes of the lungs were atelectatic, and marked congestion was noted on cut section. The pericardial sac was glistening. The heart weighed 400 gm. and was extremely flabby and pale. The coronary arteries were soft and patent. The spleen showed heavy fibrin deposits over the surface but was otherwise not remarkable. The liver presented a "nutmeg" appearance and weighed 1650 gm. The adrenal glands, pancreas, kidneys, and testes were essentially normal. Grossly, the esophagus was normal. The remaining gastric mucosa was soft and edematous, and the suture line showed several openings with ulceration. The remaining intestinal tract was not remarkable.

Microscopic Findings. The lungs were not unusual except for pulmonary congestion. There was a considerable amount of edema in the myocardium and there were focal areas of degeneration of the myocardial fibers with increased interstitial cellular elements. There was a moderate amount of perivascular infiltration with mononuclear and polymorphonuclear cells. There was moderate coronary artery atherosclerosis. Examination of the spleen revealed numerous subcapsular abscesses and the parenchyma was markedly congested. The liver capsule was covered with a fibrinopurulent exudate, and the parenchyma revealed a diffuse collection of granulocytes, especially about the portal areas. The pancreas and adrenal glands were not remarkable. The kidneys showed some areas of glomerular congestion, and albuminoid material was present in the tubules.

Sections taken from the periphery of one of the skin lesions showed a sudden transition of relatively normal epidermis. The base of the lesion was comprised of corium which was extremely infiltrated with granulocytes. Elsewhere, the skin showed only a few papillae and rete pegs. The striate muscle revealed marked degeneration. Some of the fibers appeared well preserved, but in other areas they were almost completely destroyed. There was a diffuse lymphocytic infiltration in the areas of muscle change. No specific collagenous degeneration was noted.

Case 2. This 58-year old white male was admitted to the hospital on May 28, 1951, complaining of generalized muscle pain, weakness and swelling of the hands, face and legs. In 1930 he developed classical symptoms of diabetes mellitus and had taken insulin since that time. Since 1939 he had faithfully followed a weighed diet and had been taking from 40 to 50 units of protamine zinc insulin daily. Beginning on April 15, 1951, he changed to NPH-50 insulin in the same dosage, and on this program the diabetes had been under excellent control. On May 2, 1951, he awoke with severe aching pain in the entire left arm and shoulder with associated swelling of the hand and forearm. This persisted, and about 3 days later spread to involve the right arm. He noted weakness of both arms and hands. On May 15 he noted similar soreness and weakness followed by swelling in the hips which slowly progressed to involve both legs. He had difficulty in walking and noted that "the muscles were slow to respond." By May 21 he had swelling of the face and eyes. There was no history

of recent infections, chills or fever. Two of his mother's brothers had diabetes mellitus.

Examination revealed a well developed, well nourished, sallow white male lying uncomfortably in bed. There was generalized facial swelling with periorbital edema. The blood pressure was 126/64, the pulse was 100 and the temperature was 99.4°F. The heart was of normal size and the tones were not unusual. No murmurs were heard. There were a few fine to medium resonant rales in the left lower posterior lung field. The liver was palpable 2.0 cm. below the rib cage on inspiration. The abdomen was otherwise normal. In the left axilla there was a firm, movable, non-tender lymph node, measuring

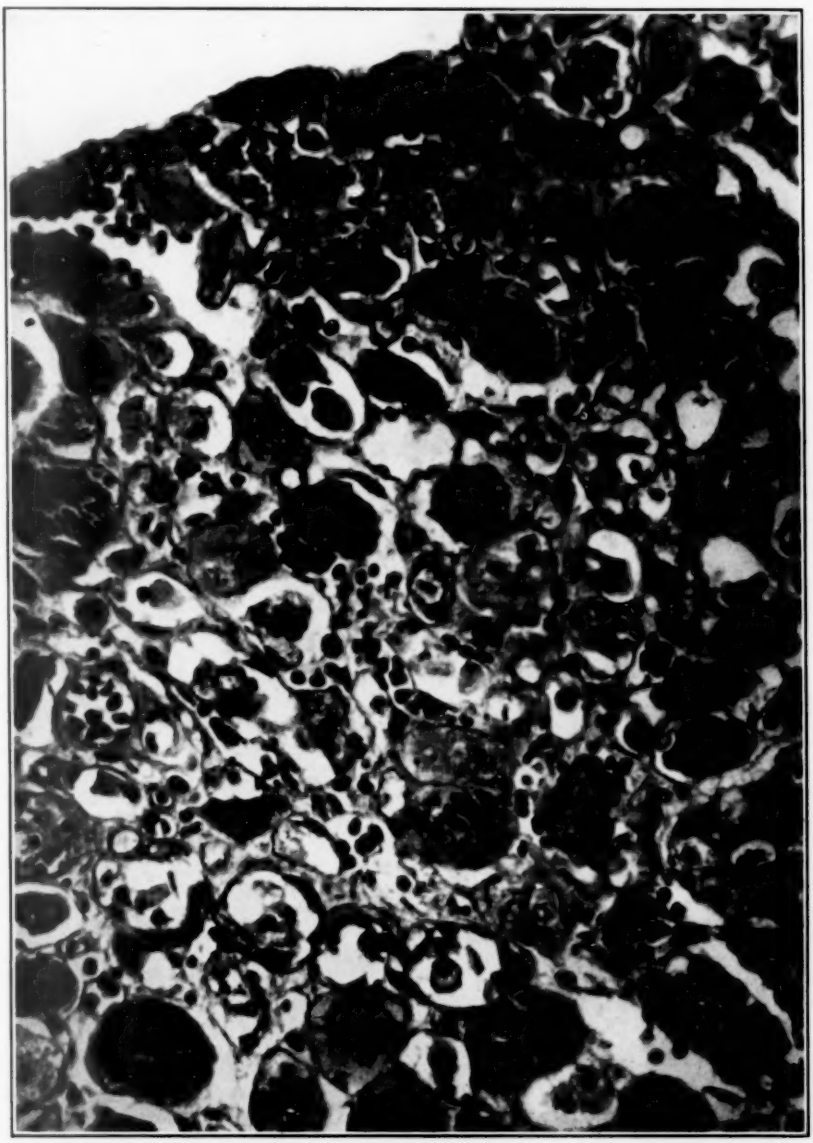

FIG. 2.—Case 1. Striate muscle as found at autopsy showing marked degenerative changes. X100.

about 2 by 1 cm., but no other lymphadenopathy was found. There was generalized edema. The fingers revealed tightness of the periarticular tissues, and there was joint tenderness on passive motion. Rather severe muscle tenderness was present in the hamstring group, the gastrocnemii, the paraspinal muscles, and those of the shoulder girdle and arms. Neurologic examination revealed absence of the deep tendon reflexes in the upper extremities and very diminished deep tendon reflexes in the lower extremities.

Laboratory findings were as follows: The serological test for syphilis was negative. Urinalysis showed a specific gravity of 1.022, reduction negative, one to two plus albuminuria, occasional granular casts, and no red blood cells. Porphyrins were negative. The red cell count was 3,530,000 and the hemoglobin was 11.5 gm. The white cell count was 9,350, and the differential count showed 58% polymorphonuclear neutrophils, 8% band cells, 32% lymphocytes and 1% basophils. The uncorrected sedimentation rate was 49 mm. in 1 hour (Wintrobe). The blood urea nitrogen was 21 mg. Total serum proteins were 5.2 gm., with 2.7 gm. of albumin and 2.5 gm. of globulin. Total cholesterol was 118 mg., and cholesterol esters were 112. Serum calcium was 8.5 mg., inorganic phosphorus 3.85 mg., and serum acid and alkaline phosphatase determinations were normal. The blood sugar was normal, and urine reduction ranged from negative to a trace. An electrocardiogram was within normal limits. Roentgen examination of the chest was negative. Fluoroscopically, the heart was normal. A barium swallow under the fluoroscope revealed very slow passage through the upper one-third of the esophagus, and a large amount of barium was retained in the valleculae. An intravenous urogram revealed no abnormalities.

The patient ran a low-grade fever up to 100°F. His pulse and blood pressure remained normal. The diabetes was easily controlled by diet and 30 units of NPH-50 insulin, which was later changed to a mixture of protamine zinc and regular insulin. In spite of the absence of skin lesions, it was felt that a clinical diagnosis of acute dermatomyositis was justified. On June 7 he was given 100 gm. of human serum albumin intravenously over a 20-minute period. Five minutes after completion of the infusion he abruptly developed a severe chill with a fever which ultimately reached 105.4°F. and cyanosis with marked asthmatic type breathing, later followed by pulmonary edema. The systolic blood pressure rose to over 200 mm. of mercury. He was treated with aminophyllin, diphenhydramine, lantoside C, tourniquets, phlebotomy and oxygen. Seven hours after completion of the albumin infusion, he had improved to the point that oxygen could be stopped, and he was able to eat his evening diabetic meal. At that time the chest revealed only occasional moist basilar rales, and his pulse and blood pressure had returned to normal. However, 8 hours after the albumin injection his respirations abruptly ceased and he expired.

Necropsy was performed on the unembalmed body 18 hours after death. There was generalized edema, most marked over the dependent portions of the body. The musculature was distinctly pale, soft and edematous, but there was no apparent atrophy. The fascial planes were extremely moist. There was a small amount of straw colored fluid in each hemithorax. The lungs were heavy, congested and edematous. There was no evidence of tumor. The thyroid gland appeared normal. The heart was of normal size. The myocardium was firm but seemed somewhat pale. There was some thickening of the mitral cusps with shortening of the chordae tendinae which was felt to be residual changes of healed rheumatic valvulitis. The spleen was not remarkable. The liver showed 6 cavernous hemangiomata which measured from 1.0 to 3.0 cm. in diameter. The pancreas was smaller than usual but maintained its usual architecture. The adrenal glands were thinned and there appeared to be a decrease in the cortical tissue. The gastrointestinal tract was not noteworthy. Within the lateral inferior portion of the left kidney there was a lobulated tumor mass which measured 4.0 by 4.0 by 4.0 cm.; there was no evidence of extension nor metastasis of this lesion (Fig. 3). There was enlargement of the lymph nodes, particularly in the paraaortic area and in the axillae, the largest node measuring 1.6 by 1.0 by 1.0 cm. The nodes tended to occur in small clusters and were firmer than normal. The remainder of the examination, including the brain and spinal cord, revealed no gross abnormalities.

Microscopic Findings. The lungs revealed only congestion and edema. There were some focal atrophy and degeneration of the myocardial fibers, associated with small areas of round cell infiltration. The liver showed a diffuse granulocytic infiltration into the sinusoids. Changes of mild intercapillary glomerulosclerosis were present in the kidneys. The renal tumor was a typical clear cell adenocarcinoma (Fig. 4). Sections of the skin generally were not unusual. One area

revealed a mixed cell pericapillary infiltration in the corium. The striate muscle revealed extensive degeneration of the muscle fibers, associated with diffuse lymphocytic infiltration (Fig. 5). The remainder of the examination revealed no noteworthy changes.

Discussion. In Case 1, the initial symptoms of the final illness were those of dysphagia, later followed by the classical findings of dermatomyositis. By the time the gastric neo-

FIG. 3.—Case 2. Left kidney showing the small, lobulated tumor mass.

plasm was discovered, the disease was too far advanced to provide any treatment other than palliation. The part played by the collagen disease in the breakdown of the surgical suture line is, of course, problematical but suggestive.

The second case presents the picture of diabetes mellitus of many years' duration followed by dermatomyositis. The diabetic state apparently was not significantly altered by the collagen disease, which is interesting in view of the disturbance in carbohydrate metab-

FIG. 4.—Case 2. Adenocarcinoma of left kidney. X100.

olism occasionally noted in such cases[5,6]. The renal tumor was an incidental finding at necropsy, and its role in the precipitation of the dermatomyositis is a matter of speculation. Furthermore, the change of insulin from protamine zinc to NPH-50 shortly before the onset of the final illness raises another question as to the introduction of a foreign protein, although the protamine molecule would be no different than that of his pre-

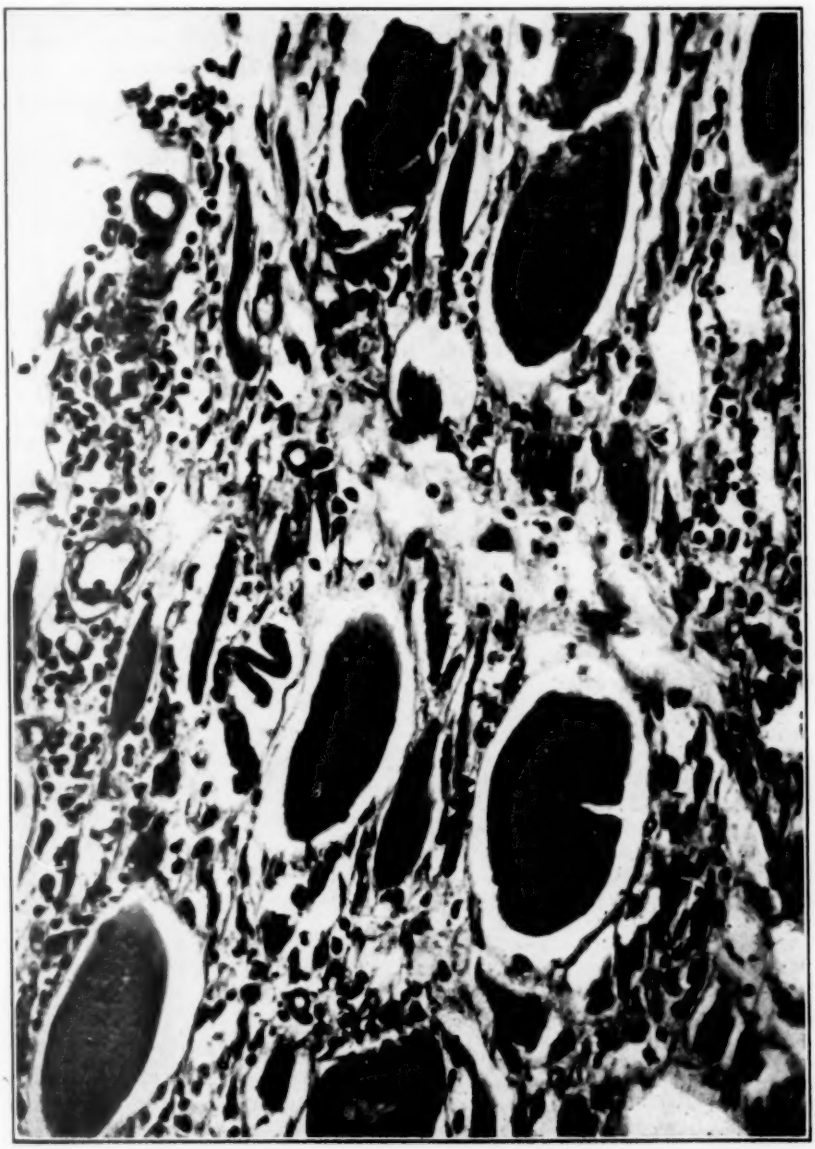

FIG. 5.—Case 2. Striate muscle showing round cell infiltration and degeneration of muscle fibers. X100.

vious insulin. Unfortunately, a sample of the human serum albumin used in this case was not available for study.

The neoplasms previously reported by Brunner and Lobriaco[2] involved the ovary, stomach, breast, reticuloendothelial system, esophagus, gallbladder, vagina and rectum. The second case herein presented is the first reported involving the kidney*.

Summary. 1. Two cases of rapidly progressing dermatomyositis are presented, in which the initial complaints were due to the collagen diseases. Later in the course of the disease, malignant neoplasms were demonstrated.

2. The possible causal relationship of tumors to some cases of dermatomyositis is again suggested.

* The Editor (RAK) has seen such a case in which an unsuspected cancer of the renal pelvis was found at necropsy in a patient who died of dermatomyositis.

REFERENCES

1. **Bezecny, R.**: Arch. f. Dermat. & Syph., **171**, 242, 1935.
2. **Brunner, M. J.**, and **Lobriaco, R. U.**: Ann. Int. Med., **34**, 1269, 1951.
3. **Cohen, S. G., Mayer, L. D.**, and **Criep, L. H.**: J. Allergy, **66**, 487, 1951.
4. **Dostrovsky, A.**, and **Sagher, F.**: Brit. J. Derm. and Syph., **58**, 52, 1946.
5. **Dowling, G. B.**: Brit. J. Derm. & Syph., **52**, 242, 1940.
6. **Griffiths, W. J.**: Brit. J. Derm. & Syph., **52**, 295, 1940.
7. **Klemperer, P.**: Am. J. Path., **26**, 505, 1950.
8. **Pagel, W.**: J. Clin. Path., **4**, 137, 1951.
9. **Rich, A. R.**: Bull. Johns Hopkins Hosp., **71**, 123, 1942.
10. **Rich, A. R.**, and **Gregory, J. E.**: Bull. Johns Hopkins Hosp., **72**, 65, 1943

EFFECTS OF PRESSURE BREATHING ON VENOUS PRESSURE; A COMPARATIVE STUDY OF POSITIVE PRESSURE APPLIED TO THE UPPER RESPIRATORY PASSAGEWAY AND NEGATIVE PRESSURE TO THE BODY OF NORMAL INDIVIDUALS

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The purpose of this paper was to determine the venous pressure response of human subjects during artificial respiration produced (1) by the tank respirator, (2) by means of a positive pressure mask or the Emerson positive pressure dome attachment to the respirator, and (3) a combination of negative and positive pressures in the respirator. In the studies of Maloney and Whittenberger[8,11] negative pressure applied to the body, as in the tank respirator, was considered to produce similar physiologic effects as positive pressure applied to the upper respiratory passageway. The clinical advantages as well as the hazards of mask pressure breathing could thus be initiated by conventional operation of the tank respirator.

Since the venous pressure was found to rise to a variable extent as a compensatory response to pressure breathing, approximately 40% above control levels in normal subjects and 70% in patients with cardiac insufficiency[2], observations were carried out on the same subjects with the various methods of mechanical ventilation studied. The elasticity of the lungs and surrounding structures appeared to be the main factor which determined the degree of pressure transmitted to the chest and hence the increment in venous pressure.

Methods. Graphic records were obtained of air pressures in the tank type respirator, the Emerson positive pressure dome and the Bennet positive pressure mask. The Statham differential transducer was used as a pick-up unit for the pressure differential between the atmosphere and the ambient intra-tank pressure. In reporting the changes in tank pressure, the atmospheric pressure was used as the zero reference point. A Sanborn strain gauge amplifier and Viso-cardiette served as a recording unit. All curves were analyzed for inspiratory, expiratory and mean pressure. The latter were determined by means of planimetric analysis of the complete respiratory cycle.

The same instruments were used to determine venous pressure. When experiments were conducted with the subject in the respirator, the venous pressure was recorded relative to the ambient intra-tank pressure since the subject's body and, therefore, the bulk of the circulatory system was exposed throughout the experiment to the intra-tank

atmosphere, only the head being outside the respirator. Venous pressures obtained during dome or mask respirations were in reference to the room atmosphere. Normal subjects and patients with miscellaneous disease were used as subjects.

Results. Analysis of the pressure obtained during operation of the tank type respirators, the positive pressure dome, and the Bennet positive pressure mask showed considerable differences in the shape of the pressure curves and, therefore, in mean pressures, even with identical peak pressures, as seen in Table I and Fig. I.

The rise in venous pressure which took place with pressure breathing varied for the most part with the degree of pressure change, whether produced by ventilation with the tank or dome. At peak negative pressures of 20 cm. H_2O (mean pressure 6.3 cm.) and 15 cm. H_2O (mean pressure 4.4 cm.) in the Emerson tank respirator the average increase in venous pressure of 12 subjects was 22 mm. H_2O and 17 mm. H_2O respectively. Intra-dome peak positive pressures of 20 cm. H_2O and 15 cm. H_2O with mean positive pressures of 4.8 cm. H_2O and 3.0 cm. H_2O, resulted in an average increase of venous pressure of 20 mm. H_2O and 17 mm. H_2O respectively. These changes are seen in the accompanying Table 2.

By using a negative pressure of 10 cm. H_2O during inspiration and a positive pressure of 5 cm. H_2O during expiration, the mean intra-tank pressure was 1.9 cm. H_2O and the mean venous pressure increase was only 3.3 mm. H_2O. With a mean intra-tank negative pressure of 0.7 cm. H_2O, attained by using an intra-tank negative pressure of 10 cm. during inspiration and a positive intra-tank pressure of 10 cm. H_2O

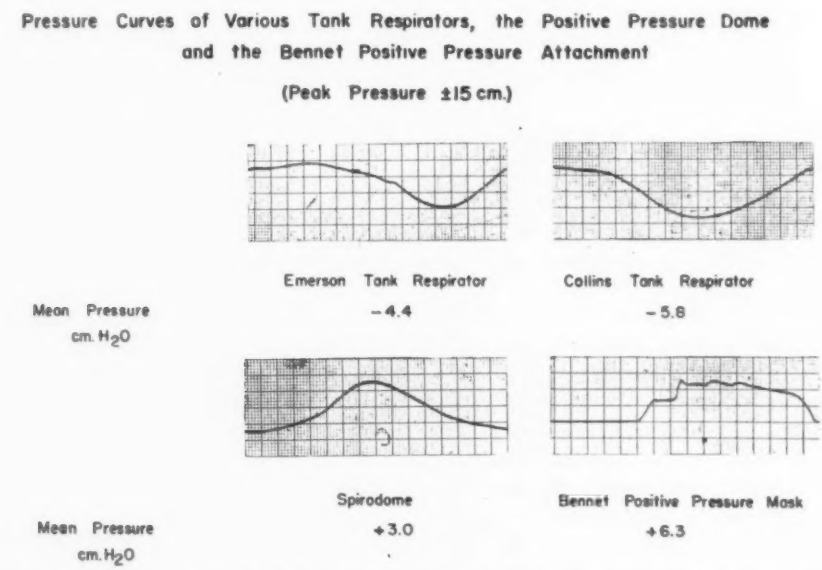

FIG. 1—Pressure curves obtained during operation of the Emerson Tank Respirator and Spirodome, the Collins Tank Respirator and the Bennet Positive Pressure Mask, at 15 cm. peak pressure have different shapes. Therefore, the calculated mean effective pressure for each method is different.

during expiration no change in mean venous pressure, within the limits of the method used, was observed, as seen in Table I.

The clinical effects of positive pressure breathing by mask and by means of negative intra-tank pressure were compared in 1 patient with pulmonary edema and 5 patients with bronchial asthma. Marked relief of dyspnea was obtained in these patients when treated with either method of pressure breathing. The sibilant rales heard throughout the lungs in the patients with bronchial asthma were diminished as soon as pressure respiration was applied by either method.

Discussion. The venous pressure response to negative pressure around the body in the mechanical tank respirator and positive pressure applied to the upper respiratory passageway was found to be similar, varying with the mean pressure applied. In the accompanying Fig. 2 an illustration of the pressure changes in the two methods of pressure breathing is presented.

At the end of inspiration in the tank respirator, the pressure surrounding the body is 740 mm. Hg when a negative intra-tank pressure of 20 mm. Hg is applied; the ambient atmospheric pressure surrounding the head is 760 mm. Hg. A flow of air is initiated by the

TABLE 1.—COMPARISON OF PEAK PRESSURES AND MEAN EFFECTIVE PRESSURES IN VARIOUS TYPES OF RESPIRATORS

Type of Respirator	*Peak Pressures cm. H_2O*	*Mean Effective Pressure cm. H_2O*
Emerson Tank	−20	−6.3
" Tank	−15	−4.4
" Tank	−10 +5	−1.9
" Tank	−10 +10	−0.7
" Dome	+20	+4.8
" Dome	+15	+3.0
Drinker Collins Tank	−20	−7.4
" " Tank	−15	−5.8
" " Tank	−10 +5	−1.5
" " Tank	−10 +10	0
Bennet Positive Pressure Attachment and Mask	+15	+6.3

TABLE 2.—VENOUS PRESSURE CHANGES DURING ARTIFICIAL RESPIRATION BY TANK RESPIRATOR (NEGATIVE INTRA-TANK PRESSURE), DOME OVER HEAD (POSITIVE PRESSURE) AND TANK RESPIRATOR (POSITIVE-NEGATIVE PRESSURE)

No. of Cases	*Intra-tank Pressure cm. H_2O*	*Change in Mean Venous Pressure mm. H_2O*
12	−20	+21.5
12	−15	+17.3
10	−10 +5	+ 3.3
10	−10 +10	+ 0.7

No. of Cases	*Intra-dome Pressure cm. H_2O*	*Change in Mean Venous Pressure mm. H_2O*
12	+20	+20.2
12	+15	+16.7

pressure gradient from the nose and mouth at 760 mm. Hg to the lungs, until an equilibrium is reached, that is, until the intrapulmonary pressure is 760 mm. Hg. At that instant the intrapulmonary pressure is 20 mm. Hg higher than the pressure surrounding the body. When a pressure increase above the atmosphere of 20 mm. Hg is used over the nose and mouth with a dome or mask, the pressure surrounding the body is 760 mm. Hg; a flow of air is then produced by the pressure gradient from the nose and mouth at 780 mm. Hg to the lungs at 760 mm. Hg until an equilibrium is reached, that is, until the intrapulmonary pressure is 20 mm. Hg greater than the pressure surrounding the body.

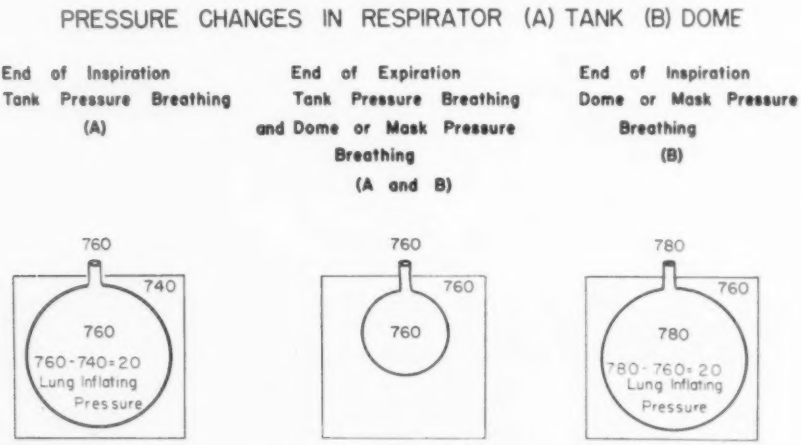

FIG. 2.—The intrathoracic pressure is 20 cm. higher than the extrathoracic pressure at the end of inspiration by negative intra-tank pressure and by positive pressure applied over the upper respiratory passageway. Each method of ventilation is due to pressure breathing.

The physiologic effects of each method of artificial respiration appear to be similar with several exceptions which appear to be of no clinical significance. The density of the gas delivered to the lungs by a pressure gradient from 780 mm. Hg to 760 mm. Hg is greater than that in the atmosphere during a fall from 760 mm. Hg to 740 mm. Hg. This factor, represented by the equation 20/760, amounts to an increase in density of approximately 3% during ventilation by pressure changes applied to the upper respiratory airway. Theoretically, an insignificant increase in turbulent viscosity would take place in obstructive dyspnea. A minor increase in oxygen tension in the atmosphere is present during upper respiratory breathing, that is, approximately 0.6%. The volume of air in the lungs is also reduced about 3% with a 20 mm. Hg pressure increase above the atmosphere as compared to a sub-atmospheric pressure of 20 mm. Hg.

In studies on the effect of pressure breathing in pulmonary edema a marked prolongation of the circulation time was noted in patients with cardiac disease in contrast to a slight and variable increase in normal subjects[2]. Subsequently, studies carried out on pressure breathing as a means of increasing altitude tolerance revealed a consistent

rise in venous pressure, proportionate to the mean pressure, whether pressure breathing was achieved by continuous or intermittent pressure[3,4,6,10]. A decrease in cardiac output was frequently observed with mean pressures of 20 cm. H_2O[6,9]. Mean pressures in the neighborhood of 6 cm. H_2O did not generally produce measurable changes in cardiac output in normal subjects. However, in patients with shock or impending peripheral circulatory failure, the hazard of pressure breathing has been emphasized as in these cases increase in intrapulmonary pressure may retard entrance of blood into the right heart[1]. Whittenberger, Sarnoff and Maloney[8,12] have also shown that pressure respiration during sympathetic depression may result in circulatory collapse because of the absence of compensatory mechanisms ordinarily evoked by increased intrathoracic pressure, such as increase in venous pressure.

The elevation in venous pressure as a result of pressure breathing constitutes, therefore, a sign of considerable importance in respect to maintenance of the integrity of circulation. Since the changes in venous pressure produced by pressure breathing over the respiratory airway are similar to those obtained when pressure breathing is accomplished by instituting a negative pressure in the tank respirator, artificial respiration with a conventional tank respirator should be considered a procedure which carries with it the advantages as well as the dangers of so-called positive pressure respiration. In the presence of an intact circulatory system, pressures within the ranges required for adequate pulmonary ventilation are not hazardous. Furthermore, in cases of pulmonary edema, pressure breathing is of value whether accomplished by a mask or tank respirator, as reported by Maloney and Whittenberger[8] and observed by us. Similarly, in 5 patients with asthma and pulmonary emphysema the use of negative intra-tank pressure resulted in the relief of dyspnea to a degree comparable to positive pressure breathing applied with a mask or hood.

In patients in whom peripheral circulatory insufficiency is present, pressure breathing is instituted with the caution previously described. If a fall in systolic blood pressure of more than 10 or 15 mm. Hg takes place, or if the pulse volume is reduced as a result of pressure breathing in the tank, modification of the procedure should be instituted by lowering the mean intra-tank pressure employed. By increasing the expiratory intra-tank pressure to a positive pressure of 6 cm. H_2O, and keeping the inspiratory pressure at minus 15 cm. H_2O, an increase in ventilation takes place above that obtained by the use of negative intra-tank pressure during inspiration of 15 cm. alone. This would result in a lower requirement for a compensatory rise in venous pressure than would be necessary for ventilation by means of an intra-tank negative inspiratory pressure of 21 cm. An even smaller challenge to the venous pressure mechanism is provoked by intra-tank pressures of plus 10 and minus 10 cm. H_2O.

In current studies, the use of a swift rise in negative intra-tank pressure to the atmosphere has been shown to result in ventilation with a less marked rise in mean venous pressure[5]. A sudden opening of a 5 inch butterfly valve was made use of to increase the flow rate of air in expiration, in order to aid in the elimination of bronchial secretions. Since the mean pressure was lowered with this form of pressure breathing, the venous pressure rise was correspondingly less, that is, almost half that produced in normal subjects by conventional operation of the res-

pirator. The value of artificial respiration without an increase in mean venous pressure is illustrated in a patient in whom electrophrenic respiration was substituted for pressure breathing in the tank respirator[12].

Bower *et al.*[7] have reported and inequality in tidal air when pressure was applied over the airway by a mask as compared to negative pressure over the body in a tank respirator. Since reference was not made in that report to the effective mean pressures used, we made measurements which indicated that the mean pressure of the Bennet positive pressure mask is higher than that found with the standard Drinker-Collins tank respirator, the values being minus 5.8 cm. H_2O for a negative intra-tank peak pressure of 15 cm. H_2O as compared to 6.3 cm. H_2O for 15 cm. H_2O positive pressure in the mask. More complete filling of the lung would be expected as the result of higher mean pressures, especially in the presence of obstruction in the respiratory passageway.

Summary. 1. The venous pressure response of human subjects to pressure breathing produced by positive pressure applied to the upper respiratory passageway, by mask or dome, was compared to the effect of negative pressure surrounding the body in the conventional tank respirator.

2. When equivalent mean pressures were employed, the rise in venous pressure was of similar magnitude with each method of mechanical ventilation. The effects on the circulation were considered physiologically similar whether pressure was applied by lowering the intra-tank negative pressure or increasing the pressure applied over the nose and mouth.

3. When pressure breathing was maintained in the tank respirator by a combination of negative and positive pressures, the mean effective pressure was correspondingly lowered with a parallel decrease in venous pressure elevation. In conditions of peripheral circulatory failure, in which tank respirators are employed, advantage may be taken of the increment in ventilation that is produced by adding intra-tank positive expiratory pressure to the intra-tank negative inspiratory pressure.

4. In patients with bronchial asthma negative intra-tank pressure respiration resulted in a relief of dyspnea similar to that obtained by positive pressure breathing instituted over the upper respiratory passageway.

REFERENCES

1. **Barach, A. L.**: Physiologic Therapy in Respiratory Diseases, Philadelphia, J. B. Lippincott Co., 1948, p. 108.

2. **Barach, A. L., Martin, J.,** and **Eckman, M.**: Ann. Int. Med., **12**, 754, 1938.

3. **Barach, A. L., Fenn, W. O., Ferris, E. B.,** and **Schmidt, C. F.**: J. Aviat. Med., **18**, 73, 1947.

4. **Barach, A. L., Eckman, M., Ginsburg, E., Rumsey, C. C., Jr., Korr, I., Eckman, I.,** and **Besson, G.**: J. Aviat. Med., **17**, 240, 1946.

5. **Barach, A. L., Beck, G. J., Bickerman, H. A.,** and **Seanor, H. E.**: Trans. Assn. Am. Phys., **64**, 360, 1951.

6. **Bickerman, H. A.,** and **Beck, G. J.**: Bull. N. Y. Acad. Med., **26**, 410, 1950.

7. **Bower, A. G., Bennett, V. R., Dillon, J. B.,** and **Axelrod, B.**: Ann. West. Med. and Surg., **4**, 561, 1950.

8. **Maloney, J. V., Jr.,** and **Whittenberger, J. C.**: Am. J. Med. Sci., **221**, 425, 1951.

9. **Motley, H. L., Cournand, A., Werko, L., Dresdale, D. T., Himmelstein, A.,** and **Richards, D. W.**: J. Am. Med. Assn., **137**, 370, 1948.

10. **Otis, A. B., Rahn, H.,** and **Fenn, W. O.**: Am. J. Physiol., **146**, 307, 1946.

11. **Whittenberger, J. L.,** and **Maloney, J. V., Jr.**: Dis. Chest. To be published.

12. **Whittenberger, J. L.,** and **Sarnoff, S. J.**: Med. Clin. N. Amer., **34**, 1335, 1950.

CARDIOVASCULAR AND METABOLIC EFFECTS OF CORTISONE, HYDROCORTISONE AND OTHER STEROIDS IN THE RAT*

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When administered under specific conditions, some hormonally active steroids have effects on the cardiovascular system which deviate notably from their assumed physiological activities. Thus, DCA (desoxycorticosterone acetate) is potentiated in its hypertensive effect on human beings by adrenalectomy[12] or Addison's disease[26]. From such observations, it has been inferred that some part of the normal secretion of the adrenal cortex is antipressor. Disparities between the activities of DCA and cortisone have suggested to some that the hypothetical adrenal cortical antipressor might be a steroid with the properties of cortisone. Unfortunately, studies of the cardiovascular effects of cortisone[10,13,28], Lipo-adrenal extract, Upjohn[8,9,11] and 17 - hydroxy - 11 - desoxy - corticosterone (compound S or desoxocortisone)[1,11,21,29] have been contradictory or inconclusive.

The experiments here reported were designed to resolve these issues by studies of the effects of the substances named and of hydrocortisone upon cardiovascular and other functions; we have also examined in parallel studies the properties of pregnenetriolone and of 17-hydroxy-progesterone in order to determine the specific effect of steroid hydroxylation at C-17.

Metabolic and cardiovascular functions evaluated in most of the experiments, included body weight and well-being, arterial pressure, urine flow, blood and urine composition, including urinary corticoids, and, at autopsy, gross and microscopic changes in tissues.

Methods. Female rats (70 to 100 gm. body weight) were uninephrectomized and divided into 13 groups (12 experimental and 1 untreated control). They were kept in metabolism cages, fed Purina fox chow and given 1% NaCl as drinking water. The substances administered to the experimental groups were DCA, Lipo-adrenal extract, Upjohn, cortisone acetate (Cortone, Merck, hydrocortisone acetate (Hydrocortone, Merck), Δ^4-pregnene 17α, 20, 21-triol-3-one-diacetate (pregnenetriolone), 17 - hydroxy - 11 - desoxy - corticosterone acetate (compound S) and 17-hydroxy-progesterone. The DCA was given by subcutaneous implantation of two 35 mg. pellets; Lipoadrenal extract, Upjohn, was injected subcutaneously twice daily in doses of 0.2 cc. (equivalent to daily doses of 16 rat-growth units or to glycogenic activity of 0.4 mg. of cortisone); water suspensions of cortisone and hydrocortisone acetates were given in daily doses of 2.5 mg. and of the other steroids in doses of 5 mg. daily. In addition to the observation on the effects of treatment with single steroids, every one except compound S was administered in conjunction with DCA.

Urine flow was measured daily; arterial

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pressures were determined by a tail plethysmograph[16] or from the foot pulse[25] at least once a week. Urinary protein content and outputs of formaldehydogenic urinary corticoids (FC) were determined at intervals. For FC assay, urine was collected under chloroform, pooled to a volume of 300 cc., adjusted to pH 4.5 for incubation with β-glucuronidase[3] and subsequently brought to pH 1 for extraction and measurement of FC as TFC (total FC)[2].

In the doses given, compound S, pregnenetriolone and 17-hydroxy-progesterone had no effect on growth, blood pressure, blood constituents and organ weights. Pregnenetriolone and 17-hydroxy-progesterone, like compound S[11,21], did not modify the functional or morphological effects of treatment with DCA. Data pertaining to these experiments are therefore omitted from the tables.

TABLE 1.—EFFECTS OF VARIOUS STEROIDS ON BODY WEIGHT AND ARTERIAL PRESSURE

	No. of Rats			*Body Weight in gm.*		*Blood Pressure in mm. Hg*	
Group	*Initial*	*Final*	*Treatment*	*Initial*	*Final*	*10th day*	*20th day*
1	8	8		86 (72–102)	147 (112–170)	121 (100–145)	119 (102–145)
2	8	7	DCA	90 (78–100)	130 (114–176)	128 (112–155)	154 (120–170)
3	8	4	Cortisone	85 (70–100)	80 (68–95)	140 (102–160)	132 (120–150)
4	7	6	Hydrocortisone	89 (72–103)	85 (62–112)	143 (126–155)	142 (110–160)
5	4	4	Lipo-adrenal Extract	90 (85–98)	140 (130–157)	123 (110–135)	111 (90–120)
6	14	2	DCA Cortisone	88 (78–98)	78 (74–88)	159 (110–170)	142* (140–145)
7	8	5	DCA Hydrocortisone	97 (83–106)	87 (60–82)	154 (130–170)	166 (142–200)
8	8	6	DCA Lipo-adrenal Extract	91 (75–102)	115 (66–142)	123 (110–135)	137 (112–190)

* Blood pressure taken on 2 animals on the 16th day

The experiments were terminated by sacrifice either on the 30th day or as required by lack of steroid in the case of 17-hydroxy-progesterone or by reason of excessive mortality (concurrent DCA + cortisone). The animals were lightly anesthetized and heparinized; the blood was collected for analysis; the tissues selected for study were placed in Zenker's fluid or 10% formalin, weighed and sectioned. The brain was removed immediately, weighed and prepared for determination of the thiobarbituric acid index[4], which has been claimed to correlate with the level of adrenal cortical activity[33].

Results. The more significant results are summarized in Tables 1 and 2.

1. Growth and Well-being, (Table 1.) Normal growth was observed only in Group 5 (Lipo-adrenal extract, Upjohn); growth was somewhat retarded in animals given DCA alone or with Lipo-adrenal extract, more so toward the end of the experiment as hypertensive vascular disease increased in severity; growth was definitely depressed in other groups. Mortality was most severe in rats given DCA plus cortisone (Group 6); only 2 of 14 animals

were still alive on the 16th day. Cortisone (Group 3) given alone caused weight loss, but half the animals survived to the 30th day. Similarly, animals given hydrocortisone plus DCA (Group 7) showed a greater mortality than those given hydrocortisone alone (Group 4), although the corresponding mortalities were less than with cortisone. Death in the groups given cortisone alone or hydrocortisone alone was associated with extreme cachexia and infection, notably lung abscess; in Groups 6 and 7, in which these compounds were given with DCA, infection and weight loss were associated with gross hematuria and/or sudden onset of anasarca. These latter manifestations were independent of cachexia and infection and appeared suddenly at any stage of the experiments. In this respect the combination DCA + hydrocortisone was less toxic than DCA + cortisone.

TABLE 2.—EFFECTS OF VARIOUS STEROIDS ON URINE FLOW, URINARY PROTEINS AND CORTICOSTEROIDS, AND THIOBARBITURIC ACID TEST

Group	*Urine Flow* in cc. per 24 hrs.*	*Urinary Proteins in mg. per 24 hrs.*	*Urinary Corticoids in mcg. per 24 hrs.*	*Thiobarbituric Acid test values × 100*
1	8	3.4	.5	196 (170–212)
2	33	25.	1.2	176 (132–231)
3	11	4.4	1.3	219 (183–268)
4	10	5.8	1.3	
5	15	3.8	.5	243 (229–263)
6	80	140.	20.	163 (160–165)
7	60	51.4	19.	
8	45	16	3.	181 (173–197)

* Mean for the last 10 days

2. URINE FLOW (TABLE 2.) Among the groups receiving single steroids, urine flow was most increased by DCA, Lipo-adrenal extract also augmented DCA diuresis.

3. ARTERIAL PRESSURE (TABLE 1.). Arterial pressure was regularly and progressively increased in the DCA group; the other steroids, with the exceptions of cortisone and hydrocortisone, had no effect on this function. Animals given cortisone and hydrocortisone alone exhibited means of arterial pressure ranging from 131 to 143 mm. Hg while the range in controls was from 119 to 129. These determinations were reproduced by different observers and by two methods of measurement during the course of the experiment.

In rats given DCA alone, the arterial pressures persist within normal limits until about the 10th day, when there begins a progressive rise into hypertensive levels. In contrast, the small but reproducible and definite rise of arterial pressure induced by cortisone or by hydrocortisone appeared about the 5th day of steroid administration and persisted thereafter at that level. Compound S (5 mg. daily) did not affect arterial pressure (mean of group pressures 128 mm. Hg, range 105 to 140 on the 30th day).

DCA-induced hypertension was not altered by administration of other steroids with the exception of cortisone and hydrocortisone. The latter compounds seemed to accelerate the onset of DCA hypertension; thus, in a recent experiment not included in the table, 6 rats were given DCA alone for 15 days at which time the group mean pressure was 140 mm. Hg; cortisone (2.5 mg. daily) was given for 5 days, at the end of which time the mean group pressure was 201 mm. Hg and some of the animals manifested anasarca. As might be expected, the advance of cachexia or the onset of severe infection or of hematuria resulted in a decrease of arterial pressure.

4. Blood and Urine Chemistry. Among the substances administered singly, DCA was the only one to cause increases in blood hemoglobin and hematocrit, slight elevation of blood urea nitrogen, increase in plasma Na and decrease in plasma K. Normal values for these constituents were observed in rats treated with cortisone and hydrocortisone alone; thus, means of determinations were Cl, 106 and Na 139 mEq. per 1. after cortisone, and 108 and 135 mEq. per 1. in controls. The samples obtained from animals treated with these 2 steroids in combination with DCA were insufficient for these analyses. However, ascitic fluid of rats of Group 7 which had gone into anasarca yielded the following means: Cl, 121, Na, 145, K, 3.6 mEq. per 1. and urea nitrogen 92 mg. per 100 cc.

Analyses of urinary proteins and corticoids and of brain thiobarbituric acid index are summarized in Table 2. DCA augmented proteinuria; superimposed treatment with cortisone or hydrocortisone added to this effect, both as regards concentration and output of urinary protein. Cortisone or hydrocortisone had no effect on proteinuria when given alone.

Total urinary formaldehydogenic corticoid outputs were so low that technical errors might account for variations around the control mean of the order of 200%. However, the differences in outputs as between Groups 6, 7 and 8 and the controls are such as to indicate that steroid administration increased TFC outputs. These differences were reproduced in 3 series of tests. The augmentation of output is evident when two formaldehydogenic steroids are given concurrently; it is noteworthy that a biologically inactive formaldehydogenic steroid such as pregnenetriolone increases TFC output when given during administration of DCA to 22 micrograms (mcg.) daily (pregnenetriolone alone 1.4 mcg., DCA alone 1.2 mcg. daily).

The thiobarbituric acid indices of brain tissue varied widely in each of the groups. The mean value is increased in Groups 3 and 5 (Lipo-adrenal extract and cortisone); although we are not persuaded that these differences are significant, it may be that the normal, or low mean values in Groups 6 and 8 indicate inhibition by DCA of the stimulating effects of Lipo-adrenal extract and cortisone. Surprisingly, the mean index in rats given pregnenetriolone + DCA was elevated to 222 (range 168-312).

5. Morphological Changes. As would be expected, relative kidney and heart weights were increased by administration of DCA alone (1.27 and 0.43 gm. per 100 gm. body weight respectively; 0.73 and 0.31 gm. in controls); the combination DCA + cortisone exaggerated this effect (1.51 and 0.55 gm. per 100 gm. respectively). Absolute kidney and heart weights were not increased by administration of either cortisone or hydrocortisone alone; the increases in relative kidney and heart weights (0.93 and 0.45 gm. per 100 gm. with cortisone, 0.91 and 0.42 gm. per 100 gm. with hydrocortisone) are largely attributable to loss of body weight.

Absolute adrenal weight was greatly decreased by cortisone (10 mg.) and hydrocortisone (11 mg.) and moderately by DCA (22 mg.). The other steroids, including compound S (27 mg.) and Lipo-adrenal extract (32 mg.) had no effects on this function.

The thymus was completely atrophic in rats given cortisone or hydrocortisone; spleen weights in these groups were decreased respectively to 0.41 and 0.46 gm. (0.94 in controls). Ovaries and uterus were atrophic in animals given DCA alone or in combination. In contrast, weights of these organs were not decreased by administration of cortisone or hydrocortisone; rather, these organs were found to be well maintained at autopsy, even in the presence of severe cachexia and the uterus was in full estrus phase.

The renal lesions produced by administration of DCA require no further description; such were present in varying degrees in all groups treated with DCA; they were not substantially modified by concurrent administration of other steroids. Lesions were somewhat less severe in Groups 6 (cortisone + DCA) and 7 (hydrocortisone + DCA); this is attributable to the shorter course of the experiments (Group 6) and to wasting and cachexia (Groups 6 and 7). None of the steroids other than DCA elicited DCA-like lesions in the kidney.

The most profound pathological changes were found in Groups 6 and 7. These were largely infectional and consisted of lung abscesses, empyema thoracis and purulent pericarditis. The lungs were firm and distended, beefy red and spotted by yellowish abscesses. Those animals which had manifested hematuria showed focal intrarenal hemorrhages; the large size of these and their tendency to occur in the corticomedullary zone and medulla contrast with the flea-bite cortical hemorrhages caused by DCA alone. The renal tubules in hemorrhagic areas contained blood and sometimes pigment casts.

Kidneys of animals of Groups 6 and 7 showed under high magnification characteristic changes. These seem to represent specific effects of the combinations DCA + cortisone and DCA + hydrocortisone, since they were not seen in animals treated with any of these steroids singly, (Figure 1 a and 1 d). They consisted of deposits of homogeneous material in the capsular spaces of the glomeruli; this material stained bluish-red with hematoxylin-eosin-methylene blue, bright red with trichrome and blue with periodic acid-fuchsin. The deposits first appeared as crescents which adhered to the capsular epithelium (Figure 1 b) and went on to fill the capsular space and to cause compression atrophy of the glomerular tuft (Figure 1 c). The same deposit sometimes appeared within the capsular membrane and around the hilus of the glomerulus. Similar deposits were found in the myocardium, the muscle fibers of which in the zones of deposition lost their striations and became necrotic (Figure 2 a). The distribution of the deposits is consistent

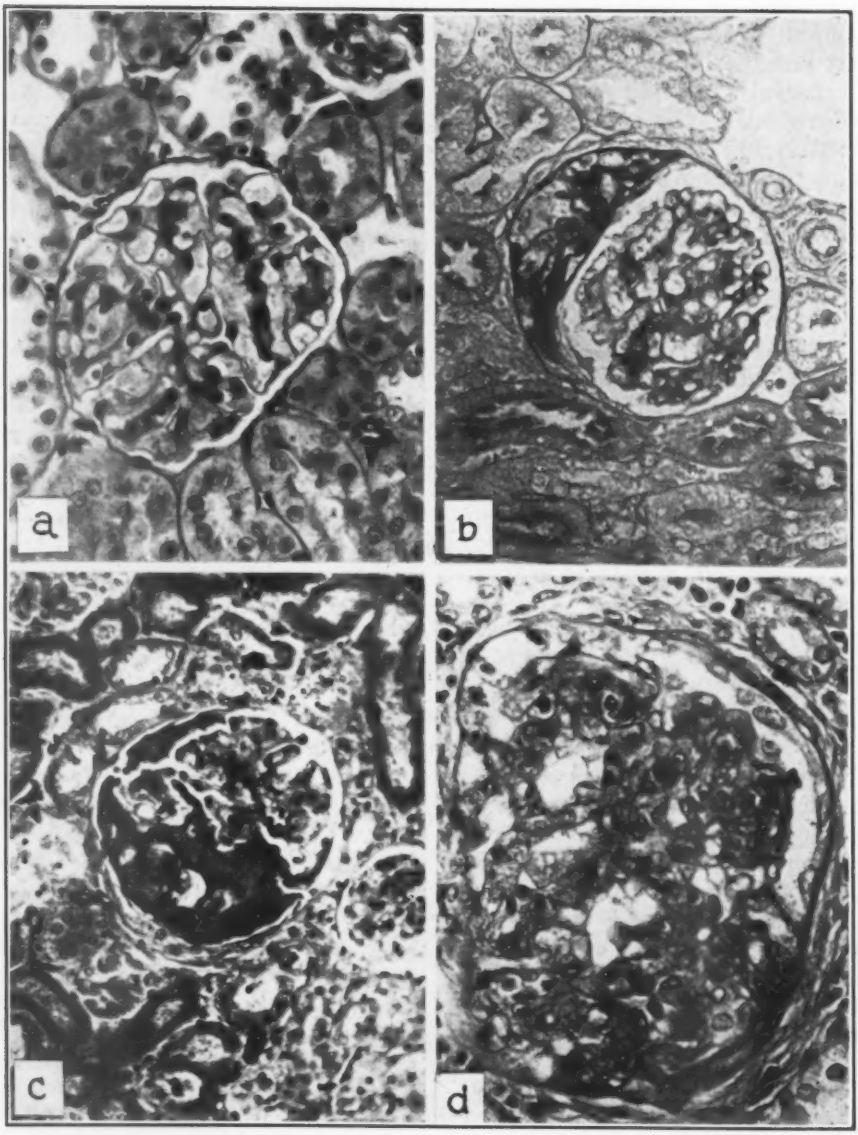

FIG. 1. (a) Normal cortical glomerulus and tubules of rat treated with cortisone (Group 3) x 400. Periodic acid-fuchsin stain.

(b) and (c). Similar sections of rats treated with cortisone + DCA (Group 6) x 400. (b). Periodic acid-fuchsin stain demonstrating a positive reaction in a crescent in the capsular space. (c) Trichrome stain: massive accumulation of the same glucoprotein surrounding and compressing the glomerular tufts.

(d) Glomerulus of rat treated with DCA alone (Group 2) x 400 Periodic acid-fuchsin stain. Cellular proliferation and hypertrophy of the endothelium of the glomerular tuft and capsular membrane with formation of synechiae. Note absence of protein material from the capsular space.

with the view that this polysaccharide-containing protein may have originated in transudation of plasma protein, a concept supported in a degree by the observed increase in proteinuria.

Some of the animals which survived treatment with DCA alone to the 30th day showed mesenteric arteritis[22]. The severity of these lesions was not influenced by concurrent treatment with the other steroids given over this time, or by Lipo-adrenal extract. The absence of these lesions in Groups 6 and 7 seems attributable to the brief course of experiment and cachexia.

The shortcomings of the experiments in Groups 6 and 7 as tests of the protective or curative effects of cortisone and hydrocortisone on DCA-vascular disease led us to devise the following experiment. Twelve uninephrectomized rats were divided into 2 groups, given each 2 implants of DCA and maintained on 1% NaCl as drinking water. DCA uptake from the pellets was supplemented by weekly injections of 10 mg. DCA in aqueous suspension. The presence of gross vascular lesions was verified by laparotomy and biopsy of the pancreatic or mesenteric arteries on the 35th day of the experiment. Cortisone was then given to 1 group of 6 rats and hydrocortisone to the other, both in daily doses of 5 mg. The course of urine flow in these groups confirmed the observations described above for Groups 6 and 7: urine output averaged 35 and 36 cc. in the 2 groups during treatment with DCA alone; on the 5th day of combined treatment mean flow had increased to 70 cc. in the cortisone group and 49 cc. in those given hydrocortisone. Over the same period arterial pressure increased from 197 to 220 mm. Hg after cortisone and 185 to 199 mm. Hg after hydrocortisone.

Rats of each group were sacrificed daily in series, beginning on the 5th day of combined treatment. As compared with the biopsies (Figure 2 b), the first effect of treatment with either cortisone or hydrocortisone was disappearance of cellular elements from the vessel wall, which persisted as a necrotic mass which contained nuclear debris and occasional lacunae of unabsorbed necrotic exudate (Figure 2 c). This state was followed by fibrous tissue repair (Figure 2 d), in spite of which the vessels remained grossly abnormal. Thus, the effect of cortisone or hydrocortisone consists simply in a resolution of inflammatory phenomena. In contrast, the renal lesions caused by DCA were not modified by treatment with either cortisone or hydrocortisone. During the brief period of treatment, 2 rats died while survivors lost weight rapidly.

Discussion. These experiments confirm our experience with DCA as a cause of hypertension and hypertensive vascular disease in rats; compound S and 2 biologically inactive compounds (pregnenetriolone and 17-hydroxy-progesterone) are added to the list of steroids which neither mimic nor oppose the action of DCA in rats. Lipo-adrenal extract in the doses used (0.4 cc. daily) is also inactive; a dose of 1 cc. daily has been reported as preventing DCA-induced increases of blood pressure, and of heart but not kidney weight[9,11]; the masses of oil injected may have had a non-specific depressor effect.

Cortisone has been reported as inhibiting the onset of DCA hypertension, but not the renal lesions caused by DCA in rats[10] and as depressor in clinical essential hypertension[26,27]. However, it has also been found not to alter the blood pressure in renal hypertension in rats[13] and essential hypertension in human beings[5]; a survey of the field suggests that it increases arterial pressure under specific conditions of sodium intake[28], renal damage[14,31]

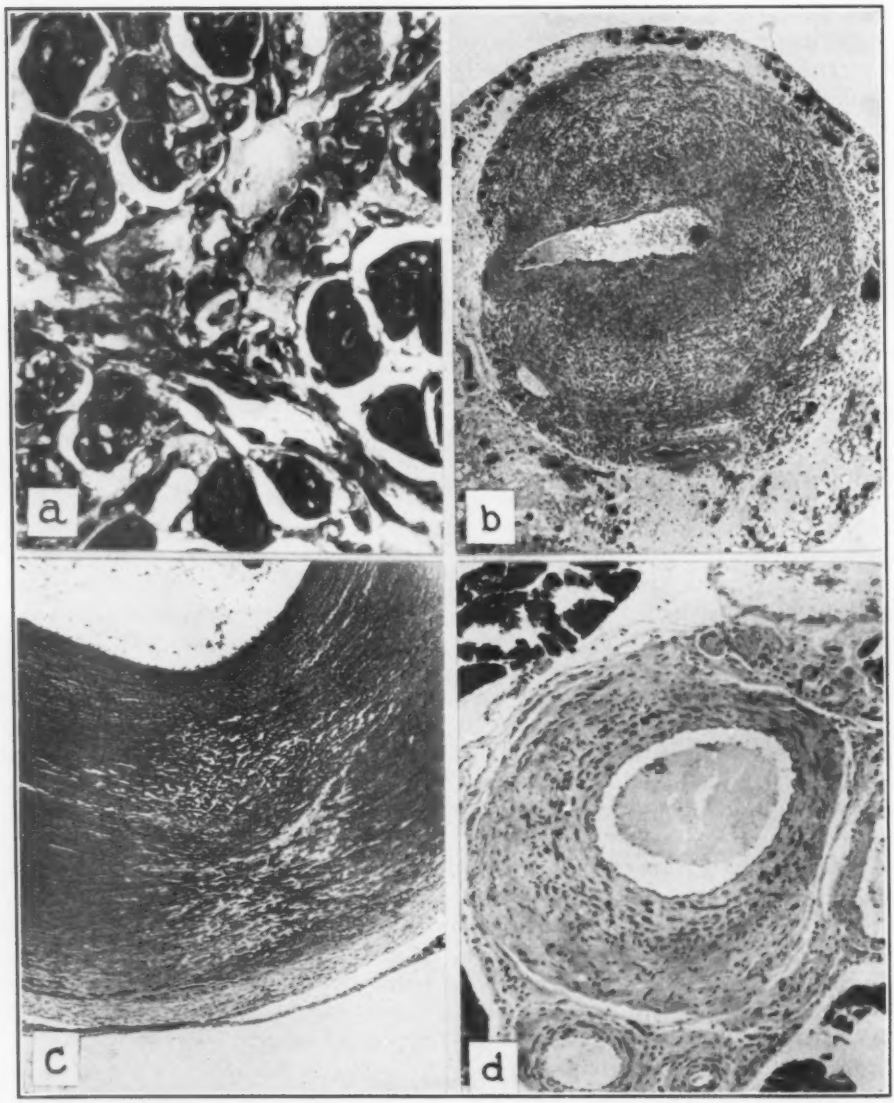

FIG. 2. (a) Myocardium of rat treated with hydrocortisone and DCA (Group 7). Phosphotungstic-hematoxylin stain x 600. Deposits of protein material surrounding necrotic and vacuolated muscle fibers. Normal fibers stain black.

(b) Pancreatic artery of a rat treated with DCA demonstrating the acute lesion of arteritis present at biopsy. Hematoxylin-eosin stain. x 100.

(c) and (d) Trichrome stain. Pancreatic arteries from rats treated with DCA and later (c) given cortisone or (d) hydrocortisone. On the 5th day of cortisone treatment, all inflammatory cells have disappeared and the wall appears as an acellular red-staining mass which contains lacunae of necrotic exudate. On the 9th day of hydrocortisone treatment, the originally diseased area, which occupied the adventitia and outer media is replaced by fibrous tissue and the only cells found are resting fibroblasts.

and deprivation of adrenal function[18]. The experiments here reported were done in uninephrectomized rats maintained on 1% NaCl; both cortisone and hydrocortisone were found to cause a small and persistent increase in arterial pressure of relatively rapid onset. This contrasts with the delayed and severe hypertension elicited by DCA. The data indicate that the slight pressor effect of these steroids is sometimes additive to the severe hypertension induced by DCA; what might be interpreted as evidence of depressor activity appear only when the animals become cachetic and widely infected. The toxicity of combined treatment with cortisone and DCA has been previously noted[23,28]; it is not solely attributable to increased cachexia and infection, but, as shown here, is associated with renal and myocardial lesions and with anasarca. DCA sensitization to a deleterious effect of cortisone brings to mind the sensitization to a toxic effect of renin-containing renal extracts also elicited by pre-treatment with DCA[24]; in both cases the lesions obtained are qualitatively different from those which result from treatment with DCA alone. It also recalls the toxicity of lyophilized anterior pituitary and of extracts thereof when given to animals treated with DCA[20]. It may have a clinical equivalent in the progressive renal damage noted in some patients with systemic lupus erythematosus[14] or renal disease[17] under treatment with cortisone or ACTH. The mechanism in each case is obscure; the lesions in DCA-cortisone or DCA-hydrocortisone treated rats seem to arise in a leakage of abnormal glycoproteins through capillary walls.

Neither cortisone nor hydrocortisone augmented urine flow when given alone, while both were unexpectedly found to increase DCA-induced diuresis. This may represent an increase in osmolarity of tissue fluids, insufficient in itself to cause polydipsia, but an adequate stimulus to animals whose hypothalamic thirst centers are already stimulated by DCA-saline treatment.

The thiobarbituric acid index of cerebral tissue has been considered an index of adrenal cortical activity[33]; enhancement of the index by Lipo-adrenal extract and cortisone and suppression of the effect by DCA are consistent with this view; the seeming effect of pregnenetriolone is not and, in each group, the variability of the index is so large and the number of observations so few as to preclude statistical evaluation. Another incidental observation is the effect of DCA in suppressing and of cortisone and hydrocortisone in maintaining ovarian and uterine weights and the estrus phase in spite of weight loss and malnutrition. This parallels similar observation made on male animals[19,32].

The significance of urinary formaldehydogenic corticoid assay in rats is not yet established, partly because of technical limitations resulting from the small amounts of material available for analysis. Normal values of urinary formaldehydogenic corticoids are much smaller than those reported by others[15] who measured reducing corticosteroids. This disparity is attributable to the ease with which rats' urine is contaminated with substances which are reducing but not formaldehydogenic. A positive finding is the augmentation, as if by synergistic action, of the output of urinary formaldehydogenic corticoids when two formaldehydogenic steroids are simultaneously administered.

We have shown that cortisone and compound F both cause resolution of the inflammatory exudate characteristic of mesenteric hypertensive arterial disease in rats, while neither remedies the nephrosclerosis caused by DCA. Since

nephrosclerosis, hypertension and intimal thickening of arteritic vessels persist and edema or intrarenal bleeding may appear as complications, the effect is therapeutic only in a very narrow sense. The evolution of the DCA-hypertensive lesions under cortisone treatment resembles the response of lesions in clinical polyarteritis nodosa[6,30] to this steroid and to ACTH.

Subcutaneous administration of hydrocortisone in water suspension has effects on arterial pressure, spread of infection, body weight, diuresis, urinary corticoids and proteins, renal lesions and hypertensive arteritis which parallel those of cortisone; in general, hydrocortisone either alone or with DCA seems somewhat less injurious to the animals than cortisone. It has recently been shown in human beings that hydrocortisone given as acetate, as in these experiments, is less active subcutaneously than orally and that the activity of the free steroid or of cortisone acetate is much the same by both routes of administration[7]. Hence the differences here noted between cortisone and compound F may reflect this property of compound F acetate and not the activity of the steroid as such.

Summary and Conclusions. A toxic action of cortisone and hydrocortisone acetates appears when these are given to animals treated with DCA; it is manifested by increased mortality, anasarca, hematuria, cachexia, infection and renal and myocardial deposits of mucoproteins; both compounds are slightly pressor and both augment DCA-induced diuresis and proteinuria; both cause resolution of the inflammatory component of DCA-hypertensive arteritis, but have no effect on nephrosclerosis.

Assays of urinary formaldehydogenic corticoids show that administration of a single steroid had little effect on this function but concurrent dosage with 2 formaldehydogenic corticoids, including pregnenetriolone, greatly augments it. Lipo-adrenal extract, cortisone and pregnenetriolone seem to increase cerebral thiobarbituric acid index, while DCA is inhibitory. Cortisone and hydrocortisone sustain uterine and ovarian weights, in spite of cachexia; these effects are suppressed by DCA.

Lipo-adrenal extract, 17-hydroxy-progesterone and pregnenetriolone did not affect the course of DCA hypertension in rats. As regards production of hypertension and vascular disease, compound S was again found to be inactive.

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REFERENCES

1. **Corcoran, A. C.:** Adrenal Cortex in Hypertension in Pituitary-Adrenal Function, The Horn-Shafer Co., Baltimore, 1950.

2. **Corcoran, A. C., and Page, I. H.:** J. Lab. & Clin. Med., **33**, 1326, 1948.

3. **Corcoran, A. C., Dustan, H.,** and **Page, I. H.**: Proc. Am. Soc. Clin. Invest., Atlantic City, May, 1951.
4. **Donnan, S. K.**: J. Biol. Chem., **182,** 415, 1950.
5. **Dustan, H., Corcoran, A. C., Taylor, R. D.,** and **Page, I. H.**: Arch. Int. Med., **87,** 627, 1951.
6. **Ehrenreich, T.,** and **Olmstead, E. V.**: Arch. Path., **52,** 145, 1951.
7. **Fajans, S. S., Louis, L. H., Conn, J. W.**: J. Lab. & Clin. Med., **38,** 808, 1951.
8. **Friedman, S. M., Friedman, C. L.,** and **Campbell, C. G.**: Am. J. Physiol., **157,** 241, 1949.
9. **Friedman, S. M.,** and **Friedman, C. L.**: Endocrinology, **46,** 367, 1950.
10. **Friedman, S. M., Friedman, C. L.,** and **Narachima, M.**: Am. J. Physiol., **163,** 319, 1950.
11. **Friedman, S. M.,** and **Friedman, C. L.**: Endocrinology, **49,** 318, 1951.
12. **Green, D. M., Nelson, J. N., Dodds, G. A.,** and **Smalley, R. E.**: J. Am. Med. Assn., **144,** 439, 1950.
13. **Grollman, A.,** and **Konnerth, A.**: Endocrinology, **48,** 213, 1951.
14. **Heller, B. I., Jacobson, W. E.,** and **Hammarsten, J. F.**: J. Lab. & Clin. Med., **37,** 133, 1951.
15. **Jarpa, A.,** and **Croxatto, H.**: Bol. Soc. Bio., Santiago de Chile, **6,** 28, 1948.
16. **Kempf, G. F.,** and **Page, I. H.**: J. Lab. & Clin. Med., **27,** 1192, 1942.
17. **Kinsell, L. W.**: Ann. Int. Med., **35,** 615, 1951.
18. **Knowlton, A. I., Loeb, E. N., Stoerk, H. C.,** and **Seegal, B. C.**: Proc. Soc. Exp. Biol. & Med., **72,** 722, 1949.
19. **Leroy, P.**: Compt. rend. Acad. Sc. (Paris), **233,** 976, 1951.
20. **Masson, G. M. C., Corcoran, A. C.,** and **Page, I. H.**: J. Lab. & Clin. Med., **34,** 1416, 1949.
21. Idem: Endocrinology, **46,** 441, 1950.
22. **Masson, G. M. C., Hazard, J. B., Corcoran, A. C.,** and **Page, I. H.**: Arch. Path., **49,** 461, 1950.
23. **Masson, G. M. C., Corcoran, A. C.,** and **Page, I. H.**: J. Clin. Endocrinol. **11,** 794, 1951.
24. Idem: J. Lab. & Clin. Med., **38,** 213, 1951.
25. **Olmsted, F., Corcoran, A. C.,** and **Page, I. H.**: Circulation, **3,** 722, 1951.
26. **Perera, G. A.**: Bull. N. Y. Acad. Med., **26,** 75, 1950.
27. **Perera, G. A.**: **Fleming, T. C., Pines, K. L.,** and **Crymble, M.**: J. Clin. Invest., **29,** 739, 1950.
28. **Selye, H.**: *Stress,* Montreal, Acta Endocrinologica Inc., 1950.
29. Idem: Brit. Med. J., **1,** 203, 1950.
30. **Shick, R. M., Baggenstoss, A. H.,** and **Polley, H. F.**: Preliminary report, Proc. Staff Meet., Mayo Clinic, **25,** 135, 1950.
31. **Sprague, R. G., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H.,** and **Polley, H. F.**: Arch. Int. Med., **85,** 199, 1950.
32. **Stamler, J., Pick, R.,** and **Katz, L. N.**: Circulation, **4,** 461, 1951.
33. **Zander, H. L.**: J. Pharmacol. & Exper. Therap., **101,** 40, 1951.

KHELLIN THERAPY IN ANGINA PECTORIS

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THE present therapy of angina pectoris is frequently most unsatisfactory as evidenced by the various medical and surgical procedures advocated for use in this disease. The evaluation of the efficacy of any treatment for angina is equally unsatisfactory due to the many factors that must be considered with each individual patient—emotional stability, the psychologic effect of any new treatment, the varying physical limits each individual will attempt, progression of the disease process, reduction of weight, the use of tobacco, and even the weather—to mention a few. In an effort to study one of the newer drugs currently used in the treatment of angina pectoris, we have treated with khellin*, the active principle of *Ammi Visnaga*, 41 cases from the Cardiac Clinic of the Pennsylvania Hospital, over a 17 months' period.

Ammi Visnaga is a plant indigenous to the Mediterranean countries. Decoctions of its seeds have been used since ancient times as an antispasmodic in renal colic[1]. In 1945 Kenawy and Barsoum[6] reported on the clinical use of khellin in angina pectoris. Seven cases were followed with promising results. Anrep, Kenawy and Barsoum reported on 250 patients with angina pectoris treated with khellin in 1948[1]. One hundred and forty (56%) of the cases had a good response to khellin (attacks ceased or very infrequent), 85 (34%) a moderate response (attacks diminished in frequency and severity) and 25 (10%) no favorable changes. Experimentally, these authors found khellin to be 4 times more effective as a coronary dilator than aminophylline without increasing the work of the heart, cardiac output or lowering the systemic blood pressure. They feel that khellin, in therapeutic dosage, acts selectively on the coronary arteries and is characterized by a cumulative and prolonged action, absence of tolerance and a wide margin of safety. Its vasodilating action is less than that of amyl nitrite but is more prolonged. Ayad[3] reported the disappearance of anginal attacks in 14 out of 23 cases (61%) with marked improvement in 5 (22%) and with no change in 4 (17%). Rosenman *et al.*[8] produced definite improvement in 11 of 14 cases of angina pectoris with moderate improvement in 1 and no benefit in 2. Armbrust and Levine[2] in a series of 53 cases, found improvement in 60%. Greiner *et al.*[5] reported no difference between khellin and the placebo in 39 patients with angina of effort.

Method of Study. The 41 patients with angina pectoris, of which 33 were male and 8 female, ranging in age between 42 and 70 years, were seen by various members of the Cardiovascular Department of the Pennsylvania Hospital usually at biweekly intervals.

* The tablets of khellin ("Eskel", 40 mg. each) and the placebo were supplied through the courtesy of Smith, Kline & French Laboratories.

The types of heart disease represented are shown in Table 1. All patients had complete blood counts, urine analyses, blood serologic tests for syphilis, electrocardiograms and orthodiagrams before starting treatment. Other laboratory studies were obtained if indicated. The electrocardiograms were interpreted as being within limits of normal in only 6 patients. Fifteen of the 41 patients had electrocardiographic evidence of previous myocardial infarction and 23 of the patients were receiving digitalis therapy. Exercise and anoxemia tests were performed in 9 cases. More frequent use of these tests was impossible because of the severity of the heart disease in the majority of the patients.

TABLE 1.—THE TYPES OF HEART DISEASE IN 41 PATIENTS WITH ANGINA PECTORIS.

Coronary	Luetic	Rheumatic	Congenital	Total
34*	5	1	1	41

* Eight of these patients also had hypertension.

TABLE 2.—RESULTS WITH KHELLIN THERAPY IN 41 PATIENTS WITH ANGINA PECTORIS.

Marked Improvement	Questionable or Slight	No Change
2(5%)	15(37%)	24(58%)

After establishing a base-line for each patient, the following criteria were used by the examiners in evaluating the response of the patients: the number and severity of the anginal attacks with the precipitating factors if known, the exercise tolerance, the number of nitroglycerine tablets used, and the general well-being of the patients while on khellin and placebo therapy. With few exceptions, because of associated illnesses, no sedatives or vasodilators, other than nitroglycerine, were administered concurrently with the khellin or placebo. Again, in almost every instance, the patient was first placed on the placebo tablets, similar in appearance to the khellin tablets, in an effort to minimize the psychologic effects of a new drug. Khellin, starting with 1 tablet 3 times a day, was then substituted after several weeks of placebo therapy.

The length of time the patients were followed varied from 6 to 66 weeks. All except a few of the cases have had at least 1 trial of placebo therapy averaging 2 to 4 weeks in duration and 17 had their khellin treatment interrupted 2 or more times with placebo therapy, without the patient's knowledge. The average time of study of the 41 patients was 33 weeks.

Results. As shown in Table 2, 2 (5%) of the 41 cases were definitely improved on khellin therapy as compared to the period when they were on placebos or before treatment was started. Both of these had severe angina and, although never entirely free from attacks, the relief they obtained, according to the aforementioned criteria, was striking. Fifteen patients (37%) showed possible or slight improvement while taking khellin. An interesting feature in several of these cases was the relief from night pain which they obtained with little or no effect on increasing their exercise tolerance or the number of nitroglycerine tablets used during the day. Twenty-four patients (58%) showed no beneficial changes while on khellin therapy. No particular type of heart disease with angina seemed more benefited than another, although it is interesting that the 2 cases with the best results were classified as having severe angina. Random blood counts on some of the patients during their course of khellin therapy showed no change over the control results. There was also no effect noted on the systemic blood pressure.

Seven of the 41 patients died during

the period of study. As mentioned by Rosenman[8], the problem of the patient increasing his activity following the relief of his pain with khellin with a resulting terminal accident may be an important one. However, only 2 of these 7 cases were at all benefited by the drug and it is not apparent from their records that any undue exertion or activity may have been a precipitating factor in their deaths.

As previously noted, a single two-step exercise tolerance and anoxemia tests were performed on 9 of the 41 patients in this series. The former was positive, according to the criteria of Master[7], in 3 cases and the latter in 1 instance. Pain did not occur in any case. A repeat exercise test on 1 of these patients while on khellin therapy remained positive. Repeat tests were not performed on the remaining cases because of the institution of digitalis therapy in 2 cases and the development of a bundle branch block in the remaining case.

Side Effects. Nausea, vomiting, dizziness and insomnia constituted the main side effects noted in this group of patients and some or all of these were prominent features in 17 (41%) of the 41 cases. This usually occurred several days after khellin therapy was begun, although a few patients complained of the untoward effects soon after the ingestion of the pills. For these reasons the patients were instructed to take the khellin following or during their meals and, in some, the dosage had to be reduced to 1 tablet twice daily. This usually sufficed to minimize, although not always eliminate, the untoward reactions. Only 1 patient was unable to follow this schedule and discontinued the treatment because of these side effects. Attempts to increase the daily intake to more than 3 tablets were usually unsuccessful due to gastrointestinal upsets. Only 1 patient was able to take 4 tablets daily over a long period of time. Rosenman[8] reported the occurrence of constipation or diarrhea, and a vesiculo-papular eruption in 1 and urticaria in another of his patients.

Comment. In our group of patients we have attempted to utilize only cases in which the disease was chronic and relatively stabilized. There is a real paucity of such patients who are suitable for clinical studies of this type. The 41 patients were chosen from a much larger initial group. The severity of the coronary disease present in such anginal patients has been stressed by Blumgart, Schlesinger and Zoll[4]. Old coronary occlusions or narrowing of 1 or more of the main coronary arteries were found in each of their 38 patients in whom angina pectoris was the primary cardiac symptom. In the majority of instances, old complete occlusions of at least 2 of the 3 main coronary arteries were found. We believe the high death rate in our series attests to the severity of the underlying disease rather than a failure of the therapeutic agent. The variations in the number of patients with angina pectoris benefited by khellin, as reported by different investigators, has been mentioned. It serves, however, to emphasize the known exacerbations and remissions of the disease, the individual variations in response to a new drug and each patient's attitude toward his disease. Thus 1 individual will attempt physical activity knowing it may precipitate an anginal attack and use nitroglycerine when the pain occurs or use it prophylactically. Another patient will recognize his physical limits and will not go beyond them, thereby avoiding the use of nitroglycerine. Likewise, nitroglycerine tablets are frequently used by various patients for attacks of nocturnal dyspnea without pain, arthritic aches, etc. As can be readily seen, therefore, there is a great lack of ob-

jective criteria in evaluating the response to any treatment in patients with angina pectoris. Exercise and anoxemia tests are of some aid but in a group of elderly clinic patients with severe angina, the majority of whom are on digitalis therapy, such tests are of limited value. The patient's well-being and his personal impression of the treatment must be relied upon to a great extent. Thus the 2 patients who showed striking improvement in our series used fewer nitroglycerine tablets, increased their exercise tolerance and subjectively felt much improved on khellin. Those with slight to moderate improvement occasionally used as many nitroglycerine tablets while on khellin as when on the placebo or on no treatment, but clinically they seemed improved or their attacks of angina were less severe and incapacitating.

The lower percentage of improved patients in this series than in some others may also be due to the longer period of investigation in a disease with exacerbations and remissions. However, a short term evaluation of this type of therapy may give misleading results. This was apparent to us when analyzing the results in our first few patients after 4 to 6 weeks of treatment. The need for a drug with a prolonged "dilating effect" is great for the treatment of patients with angina pectoris. In certain of these khellin may meet this requirement. It may even be more useful if the untoward side effects can be eliminated so that larger doses can be utilized.

Conclusions. 1. Forty-one patients with established angina pectoris were treated with khellin over a 17 months' period with marked improvement in 2 (5%), questionable to slight improvement in 15 (37%), and no beneficial effect in 24 (58%).

2. Nausea, vomiting, dizziness and insomnia were troublesome side effects in 17 patients.

3. The difficulty in evaluating any method of therapy in this disease has been emphasized. Further well controlled and prolonged clinical studies with khellin are indicated.

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REFERENCES

1. **Anrep, G. V., Kenawy, M. R.,** and **Barsoum, G. S.**: Am. Heart J., **37**, 531, 1949.
2. **Armbrust, C. A., Jr.,** and **Levine, S. A.**: Am. J. Med. Sci., **220**, 127, 1950.
3. **Ayad, H.**: Lancet, **1**, 305, 1948.
4. **Blumgart, H. I., Schlesinger, M. J.,** and **Zoll, P. M.**: J. Am. Med. Assn., **116**, 91, 1941.
5. **Greiner, T., Gold, H., Cattell, M., Travell, J., Bakst, H., Rinzler, S. H., Benjamin, Z. H., Warshaw, L. J., Bobb, A. L., Kwit, N. T., Modell, W., Rothendler, H. H., Messeloff, C. R.,** and **Kramer, M. L.**: Am. J. Med., **9**, 143, 1950.
6. **Kenawy, M. R.,** and **Barsoum, G. S.**: Gaz. Fac. Med., Cairo, **13**, 39, 1945.
7. **Master, A. M.**: Med. Clin. N. Am., **34**, 705, 1950.
8. **Rosenman, R. H., Fishman, A. P., Kaplan, S. R., Levin, H. G.,** and **Katz, L. N.**: J. Am. Med. Assn., **143**, 160, 1950.

GLUCOSE ABSORPTION FROM THE DUODENUM IN PATIENTS WITH STEATORRHEA

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It is generally agreed that carbohydrate absorption is interfered with in many of the conditions accompanied by steatorrhea, but it is difficult to determine the magnitude of the disturbance, or what part it plays in the production of the patient's symptoms or disability. Some workers have suggested that it may be of greater significance than is usually appreciated, and some even feel that it may be of more fundamental importance than the disturbance in fat absorption. Certainly in our experience it has been possible to produce great amelioration of symptoms and improvement in nutrition by measures which have not altered the patient's ability to absorb fat.

In an effort to gain further information on the subject, direct observations of the absorption of glucose from the duodenum have been made in 5 patients in whom the clinical diagnosis of steatorrhea has been confirmed by fat balance studies. Five patients who had no gastrointestinal disturbances form a control group. The method used is similar to that described by Groen[7] and the criterion used, the quantity of glucose absorbed in 30 minutes when 100 cc. of a 15% solution is left in the duodenum for 30 minutes and then aspirated.

Method of Study. Fasting patients were intubated with a two-lumen Miller-Abbott tube with an inflatable balloon containing a small amount of mercury at the tip. The balloon was inflated with 25 to 50 cc. of air when it had been seen to enter the duodenum under the fluoroscope. It was then allowed to pass along to the duodeno-jejunal flexure, a point which can be localized with some accuracy, and its further progress was arrested by taking up the slack in the tube and securing it to the patient's cheek. At the same time the balloon was inflated by a constant pressure device to a pressure of approximately 40 cm. of water. Since peristaltic activity is quite vigorous in this area it was often necessary to make further adjustments in the position of the balloon before proceeding with the test. The fluoroscope table was then tilted so that the patient's head was elevated 20 degrees from horizontal, the patient placed in the supine position and asked not to cough, move or talk. Then 100 cc. of solution containing 15 gm. of glucose were injected at the rate of 15 cc. per minute.

After 30 minutes this was aspirated, and the patient given 100 cc. of water to drink. This was repeated at 5-minute intervals until 400 cc. had been given. Continuous aspiration of the duodenum was carried out for 30 minutes and the glucose content of all the aspirated fluid measured in triplicate, using the Folin-Wu method. Specimens of gastric juice were aspirated as the tube was being withdrawn and in all cases these were found to be free of glucose.

Case Material. A. STEATORRHEA PATIENTS: *Case 1.* J.B., a 58-year old male, was admitted with a history of recurrent diarrhea for 35 years and abdominal cramps for 6 months. The patient was undernourished and severely disabled. The radiological appearance of the small bowel was suggestive of regional enteritis; the stools were benzidine positive. The fat output in stools was 30 gm. daily on an intake of 100 gm. Diagnosis: regional ileitis, with steatorrhea secondary. Therapy consisted of a low fat diet only.

Case 2. R.A., male, aged 45, was admitted

with a history of having 5 or 6 watery, foul-smelling stools daily for several years. He had a severe hemorrhagic tendency due to reduction of blood prothrombin. No specific therapy was carried out save slight restriction of fat intake. At the time of the test, the patient had been discharged from the hospital and was well-nourished, working and having little disability. On 100 gm. intake, the fat output in stools was 28 gm. daily on several widely separated occasions. Diagnosis: idiopathic steatorrhea.

Case 3. M.Z., a 28-year old male gave a history of having 3 to 5 unformed, light grey stools daily for 3 years. The fat content of his stools was 25 gm. daily on an intake of 100 gm. He was in good condition, with few symptoms at the time of the test. He was treated by dietary means only. Diagnosis: idiopathic steatorrhea.

Case 4. M.F., a 31-year old male had been discharged from the army because of chronic bronchitis. He was admitted to the hospital 3 years later because of weight loss and weakness, and having 8 to 10 bulky, offensive, unformed stools daily. The fat output in his stools was studied over a prolonged period, and varied from 11 to 32 gm. daily on 100 gm. intake. He kept having short, sharp bouts of fever, each associated with the appearance of an evanescent non-specific skin eruption. Subsequently, after he had been transferred to the Veteran's Hospital, tubercle bacilli were cultivated from 1 of these lesions. With the administration of streptomycin his diarrhea cleared, and his general condition improved greatly. However, he has since been re-admitted with tuberculosis of the spine. He was severely ill and markedly under-nourished at the time these tests were performed. Diagnosis: tuberculous enteritis or mesenteric adenitis with steatorrhea secondary.

Case 5. A.C., a 36-year old female who was admitted to the Ear, Nose and Throat Service because of uncontrollable epistaxis. This was due to a marked depletion of prothrombin, which responded to vitamin K. She gave a history of recurrent bouts of severe diarrhea in the late summer and autumn for the preceding 4 years. She had had episodes of tetany and had a macrocytic anemia. The fat output in her stools varied between 10 and 27 gm. daily. She was in good condition at the time of the test, and had been receiving 75 units of parenteral liver extract weekly. Diagnosis: idiopathic steatorrhea.

B. CONTROL GROUP. *Case 6.* Female, aged 30, no bowel symptoms, diagnosis: anxiety state.

Case 7. Male, aged 28, diabetic admitted for control of his disease. No gastrointestinal symptoms.

Case 8. Male, aged 29, convalescent from acute hepatitis. No gastrointestinal symptoms.

Case 9. Male, aged 21, convalescent from poliomyelitis. No gastrointestinal symptoms.

Case 10. Male, aged 46, convalescent from contact dermatitis, without evidence of other disease.

TABLE 1.—RESULTS OF GLUCOSE ABSORPTION TEST IN 5 CASES OF STEATORRHEA AND 5 CONTROLS

Case No.	*Glucose*		
	Injected gm.	*Recovered gm.*	*Absorbed gm.*
Steatorrhea patients			
1	15	12.5	2.5
2	15	13.4	1.6
3	15	8.8	6.2
4	15	11.0	4.0
5	15	8.0	7.0
Control cases			
6	15	1.1	13.9
7	15	2.0	13.0
8	15	2.3	12.7
9	15	3.8	11.2
10	15	0.6	14.4

TABLE 2.—RESULTS OF GLUCOSE TOLERANCE TESTS; 100 GM. *PER OS*, IN 5 CASES OF STEATORRHEA AND 2 CONTROLS

Case No.	*Fasting mg.*	*½ hr. mg.*	*1 hr. mg.*	*2 hr. mg.*	*3 hr. mg.*
Steatorrhea patients					
1	91	96	101	109	95
2	78	84	86	67	69
3	71	91	83	127	87
4	73	91	81	125	110
5	83	72	64	67	65
Control cases					
9	90	120	130	110	95
10	90	164	147	84	89

Results. The results of glucose absorption and glucose tolerance tests in the steatorrhea patients and control cases are given in Tables 1 and 2.

Incidental Findings. There was a great reduction in the motility of the stomach and duodenum in the patients with steatorrhea. It took the balloon

much longer to enter the duodenum than in the control group, and the rate of advance in the duodenum was much slower. On 3 occasions the attempt to carry out the test had to be abandoned because the balloon did not reach the duodeno-jejunal juncture in 6 hours. When the glucose solution was injected in 2 patients (Cases 3 and 4) the third part of the duodenum appeared to become much dilated and to move downward. This was not seen in the other patients.

Discussion. These results confirm those of Groen, who in 1938[8] found an impairment in glucose absorption in the upper intestine of 3 patients suffering from "deficiency states". One of these had idiopathic steatorrhea, and the others would appear to have suffered from secondary steatorrhea judging from the description of their symptoms. We have studied a smaller segment of bowel than she, confining our observations to the duodenum, while her technique includes the upper jejunum to a point which is reached by a balloon 50 cm. from the pylorus. This modification was made because we wished to study the portion of the intestine which plays the greatest part in glucose absorption[14,9,11] and because we wished to avoid a possible error introduced by variations in motility of the intestine in different subjects. This might lead to an unpredictable degree of "telescoping" of jejunum over the balloon, and thus expose variable amounts of mucosa to the solution. It is interesting to note that our control group appeared to absorb glucose more efficiently than hers, since the other conditions of the test are comparable. In her communications[7,8] normal people absorbed between 7 and 9 gm., with an average of 7.77 gm.

The relationship which these findings have to the events which occur under physiological conditions must, of course, be somewhat conjectural. The flat oral glucose tolerance test in these patients contrasted with the normal intravenous glucose tolerance curve, has already suggested that glucose absorption is delayed in patients whose steatorrhea is not of pancreatic origin, under the conditions of the test. It remains to be seen what happens to the glucose which is ingested in a normal diet, or to that which is released by the digestion of starch. It would appear logical to assume that the absorption of this too would be delayed, which would mean that glucose would reach the lower reaches of the small intestine in higher concentrations than normal, unless decreased motility compensated for the delay. In either case, it would be exposed to increased bacterial activity if one accepts the finding of Frazer[6] that the bacterial population of the upper intestine is greatly increased in these patients. The process of absorption would then be further impeded by competition with bacterial fermentation, with the production of gases and irritating end products. This would account for the fermentative nature of the stools and the distension which so frequently characterize the patient with steatorrhea. However, direct evidence on these points is yet to be obtained.

It also remains to be seen why glucose absorption in the duodenum is delayed under the conditions of this test. It seems to have been established that glucose absorption is an active process, and not a matter of mere diffusion, and that the function of the duodenum is first to dilute it to a concentration of about 5% and then to absorb it through a mechanism which involves phosphorylation[11,5,4,7,2]. The function of the stomach appears to be merely that of diluting ingested glucose to a concentration of 15% before allowing it to pass into the duodenum[13,1], so that the solution used in this experiment fell

within physiological limits. It has been shown that higher concentrations of glucose are not absorbed any more rapidly from the upper intestine[5,13,12] and that the presence of moderate amounts of fat in the intestinal contents does not affect the absorption of glucose[15].

The diversity of this small group of patients with respect to severity of illness and underlying cause makes it difficult to believe that their poor performance in this test can be explained on a nutritional basis, or attributed to a specific deficiency state. Unfortunately, the discomforts of the test have prevented us from making serial observations which might have enabled us to assess the effects of various treatments. It is interesting to note that the amount of glucose absorbed did not bear any relationship to the degree of disability the patient was suffering at the time, nor does it correlate well with the oral glucose tolerance curves obtained on separate occasions. One might draw attention to the fact that the defect in fat absorption demonstrated in the fat balance studies was not proportional to the severity of the symptoms either, since it was of the same order in all 5 patients.

Carbohydrate absorption has been investigated far more actively in celiac disease than in adult steatorrhea. One cannot be certain how far the 2 conditions can be compared, but they have a good deal in common, and it would appear likely that the disturbance is very similar, though the etiology may be different. In celiac disease a defect in glucose absorption has been noted by many workers[3,10]. It has been partly attributed to disturbances of motility of the stomach and intestine, but some degree of failure in the epithelial function is also suggested. These patients usually tolerate sugar in the diet well, but are often made worse when starch is fed.

Summary. 1. The absorption of glucose from the duodenum has been studied by means of a Miller-Abbott tube, with a balloon occluding the lumen at the duodeno-jejunal juncture.

2. Five patients with steatorrhea of various types were found to absorb significantly smaller quantities of glucose than a control group, when 100 cc. of a 15% solution was left in the duodenum for 30 minutes and then recovered.

3. The implications of this finding are discussed.

REFERENCES

1. **Abbott, W. O., Karr, W. G.,** and **Miller, T. G.**: Am. J. Digest. Dis. & Nutrition, **4,** 742, 1938.
2. **Beck, L. V.**: J. Biol. Chem., **143,** 403, 1942.
3. **Crawford, T.**: Quart. J. Med., **8,** 251, 1939.
4. **Cori, C. F.**: J. Biol. Chem., **70,** 577, 1926.
5. **Cori, G. T.,** and **Goltz, H. L.**: Proc. Soc. Exp. Biol. & Med., **26,** 433, 1929.
6. **Frazer, A. C.**: Brit. Med. J., **2,** 731, 1949.
7. **Groen, J.**: J. Clin. Invest., **16,** 245, 1937.
8. Idem: New England J. Med., **218,** 247, 1938.
9. **Karr, W. G., Abbott, W. O., Hoffman, O. D.,** and **Miller, T. G.**: Am. J. Med. Sci., **200,** 524, 1940.
10. **Macrae, O.,** and **Morris, N.**: Arch. Dis. Childhood, **6,** 75, 1931.
11. **Peters, J. P.,** and **Van Slyke, D. D.**: Quantitative Clinical Chemistry Interpretations, Vol. I, ed. 2, Baltimore, The Williams & Wilkins Co., 1946, p. 103.
12. **Pierce, H. P.**: J. Nutrition, **10,** 689, 1935.
13. **Shay, H., Gershon-Cohen, J., Fels, S. S., Munro, F. L.**: Am. J. Digest. Dis., **6,** 535, 1939.
14. **Warren, R., Karr, W. G., Hoffman, O. D.,** and **Abbott, W. O.**: Am. J. Med. Sci., **200,** 639, 1940.
15. **Wishnofsky, M., Kane, A. P.,** and **Spitz, W. C.**: Am. J. Digest. Dis. & Nutrition, **4,** 174, 1937.

ANTISTREPTOLYSIN O AND ANTIHYALURONIDASE TITERS IN HEALTH AND IN VARIOUS DISEASES*

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There has been great interest over the last decade in the measurement of antistreptolysin O in the serum of human beings for the purpose of evaluating the role of hemolytic streptococcal infection in various disease states[10]. Recently streptococcal antihyaluronidase has been estimated for similar reasons[5-7,9]. Many of these studies, particularly of antihyaluronidase, have been concerned principally with the pathogenesis of rheumatic fever.

Relatively little information is available as to the expected titers of the latter antibody in other disorders. For this reason an analysis has been made of the two antibodies as measured in the same sample of serum in 140 patients. Rheumatic fever in various stages was present in 61 of these. The remainder were examples of other conditions. The information available in this laboratory as obtained from the study of 243 normal subjects of various ages is also included.

Materials and Methods. Sera. Blood was drawn aseptically; serum was removed from the clot and stored in sterile glass tubes at −20° C. until used.** The antistreptolysin O and antihyaluronidase titers of the collected sera were determined by methods previously described[3,11]. The increments of antistreptolysin O were <12, 12, 50, 100, 125, 166, 250, 333, 500, 625, 833, 1250, and 2500 units per cc. Those for antihyaluronidase were <20, 20, 100, 500, and 2500 units per cc.

Results. Healthy Subjects. The values for the serum antistreptolysin O and antihyaluronidase titers in 243 healthy persons were available. Thirty-two of these were children, 120 were medical students, and 91 were older persons. The data are summarized in Table 1.

The antistreptolysin O level was not dissimilar in children from 5 to 7 years of age and in those from 8 to 12. The mean titer in the former group was 150 units per cc., and in the latter was 184 units per cc. The values are of the same order of magnitude but are lower than those obtained in a similar and larger group in 1947[10]. Antihyaluronidase was not present in the 2 age groups in comparable amounts. Younger children had substantially less (mean titer of 36 units per cc.) and a higher incidence of very low titers

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than did older children (mean titer of 127 units per cc.)

Previous studies[3,10,12] demonstrated that very low concentrations of these antibodies are the rule during the first years of life. Usually neither was present in measurable amounts in the serum of children from 6 to 24 months of age.

The antibody levels in healthy medical students were intermediate between the 2 groups of children. The mean antistreptolysin O titer was 102 units per cc. and the antihyaluronidase titer 58 units per cc.

The antistreptolysin titers in persons between 40 and 60 years of age were distinctly lower than those in the previous 3 groups. A decline in concentration of antihyaluronidase did not occur between the early and late adult periods.

Levels of antistreptolysin or of antihyaluronidase of 500 units per cc. were distinctly uncommon in these healthy subjects. Higher titers were not encountered at all.

Rheumatic Fever. Information obtained from a study of 61 rheumatic subjects is presented in Table 2. Thirty-seven presented various degrees of activity. The diagnosis was made on clinical grounds and many had evidence of carditis since, in the absence of this manifestation of the disease, the nature of the illness often remained in doubt. Rheumatic valvular heart disease without signs of an active proc-

TABLE 1.—ANTISTREPTOLYSIN O AND ANTIHYALURONIDASE TITERS IN HEALTHY HUMAN BEINGS OF VARIOUS AGES

Age of Subjects	Total Cases	Antihyaluronidase—units/cc.					Antistreptolysin O in units per cc.									
		<20	20	100	500	Mean	<12	12	50	100	125	166	250	333	500	Mean
Children 5 through 7 years	17	5	8	4	–	36	1	5	2	1	2	1	2	1	2	150
Children 8 through 12 years	15	—	5	8	2	127	1	—	1	—	3	6	2	1	1	184
Medical students	120	32	46	38	4	58	1	22	40	10	19	17	5	3	3	102
Adults 40 through 49 years	45	3	20	18	2	77	9	21	5	6	—	2	1	1	–	46
Adults 50 through 59 years	46	3	21	19	3	84	10	18	9	2	5	—	–	2	–	48

TABLE 2.—MAXIMUM ANTISTREPTOLYSIN O AND STREPTOCOCCAL ANTIHYALURONIDASE TITERS IN ACTIVE AND INACTIVE RHEUMATIC FEVER

Stage of Rheumatic Fever	Antibody*	Cases													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Active—Onset within 90 days. Ages 3 through 12	AST	1250	833	833	500	333	250	250	250	250	166	166	166	166	166
	AHT	500	2500	500	500	20	500	500	500	500	100	500	500	100	<20
Active—Onset within 90 days. Ages 12 through 49	AST	1250	833	833	625	625	500	500	333	250	166	166			
	AHT	2500	2500	2500	500	100	500	2500	500	2500	500	500			
Active—Duration greater than 90 days. Ages 6 through 16	AST	833	625	625	500	500	333	250	250	166	166	166	100		
	AHT	500	500	100	20	100	500	100	100	2500	100	100	20		
Inactive—For less than 24 months	AST	500	500	333	333	250	250	250	125	125	100	50	12		
	AHT	100	500	100	500	100	500	500	100	<20	20	100	<20		
Inactive—For more than 4 years	AST	333	250	250	166	166	125	50	50	50	50	12	12		
	AHT	100	20	20	500	500	100	100	500	100	100	100	20		

* AST—Antistreptolysin O in units per cc.
AHT—Antihyaluronidase in units per cc.

ess was present in 24 additional cases.

The onset of the disease had occurred less than 90 days before the first observation in 25 cases of whom 14 were children. In all of these the antistreptolysin titer was 166 units per cc. or more. Only half had levels greater than 250 units per cc. The mean antistreptolysin O titer in 14 children was 398 units; in 11 adults it was 553 units per cc. The antihyaluronidase levels were also elevated, usually to an extreme degree, so that titers of 2500 units per cc. were discovered in 5, and of 500 in 14 cases. A concentration of 20 units per cc. was the maximum level attained by 1 case, and no measurable antihyaluronidase was ever present in the serum of another, even though 3 hemolytic streptococcal infections and 1 recrudescence of rheumatic fever occurred during an 18-month period of observation.

The antistreptolysin O and antihyaluronidase titers were lower in the group whose rheumatic process had been inactive for some time. They were lowest in the cases in which the disease had been quiescent for more than 5 years. In 6 cases the antistreptolysin titer had fallen to 50 units or less per cc. while the antihyaluronidase titers remained moderately high (100 units per cc.).

Rheumatoid Arthritis. The data obtained from the serological study of 18 cases of acute rheumatoid arthritis are presented in Table 3. The clinical diagnosis was made in every instance because progressive deforming arthritis was present. Those whose illness was of short duration are of special interest.

The serum concentration of antistreptococcal antibodies was low to very low in 4 of 7 very early cases and very high in the other 3. Virtually no antistreptolysin O or antihyaluronidase was demonstrable in the serum of 4 cases of more than 6, but less than 12, months' duration.

TABLE 3.—ANTISTREPTOLYSIN O AND STREPTOCOCCAL ANTIHYALURONIDASE LEVELS IN JUVENILE AND ADULT RHEUMATOID ARTHRITIS

		Duration less than 3 mos. Case				*Duration 6–12 mos.* Case			*Duration 1–5 years* Case			
Type of Disease	*Antibody**	*1*	*2*	*3*	*4*	*1*	*2*	*3*	*1*	*2*	*3*	*4*
Active Juvenile 4 to 8 years old	AST	1250	1250	12		50	12	<12	500	125	125	12
	AHT	500	500	20		<20	<20	<20	20	500	<20	<20
Active Adult 12 to 40 years old	AST	333	50	50	<12				500	50	12	<12
	AHT	500	100	100	20				2500	20	100	20

* AST—Antistreptolysin titer in units per cc.
AHT—Antihyaluronidase titer in units per cc.

The antibody levels in 8 chronic cases were low in 5 and high in 3. Large to very large amounts of antihyaluronidase in the presence of low titers of antistreptolysin were again observed in this group.

Other Arthritic Diseases. Arthritis is a common manifestation of several syndromes that have other common facets. The antistreptococcal antibody titers in 20 cases of this category are presented in Table 4. The levels were not definitely elevated beyond the expected normal range in any of 6 cases of lupus erythematosus disseminatus or collagen disease of undetermined type. Substantial amounts of one or the other, or both, antibodies were present in all but 1. High titers were detected in 1 of 5 cases of periarteritis nodosa and very low concentrations in only 1.

The values in 5 cases of erythema nodosum were comparable to those in early active rheumatic fever. Neither

tuberculosis nor coccidioidomycosis was believed to be present as an etiological factor in any of these.

Two cases of Henoch-Schönlein's purpura were different in that antistreptolysin O titers were elevated but no measurable antihyaluronidase was demonstrated. The antibody titers were very low in 2 cases of erythema multiforme.

ACUTE GLOMERULONEPHRITIS. The antibody levels in 17 cases of typical acute glomerulonephritis were determined. The data are presented in Table 5. In each there had been an acute onset of hematuria, usually associated with hypertension and often with edema. Very often there was a history of sore throat 3 or 4 weeks before the onset of the illness. Serum for immunological study was obtained during the first month in every case.

Ten of the affected persons were children less than 14 years of age. The antistreptolysin O titers were 250 units per cc. or more in every instance, and 625 units or more in 6. The mean titer was 887 units per cc. The antihyalu-

TABLE 4.—MAXIMUM ANTISTREPTOLYSIN O AND ANTIHYALURONIDASE TITERS IN VARIOUS ARTHRITIC DISEASES

Disease	*Antibody**	*Case* 1	2	3	4	5
Lupus erythematosus disseminatus	AST	250	166	12	12	
	AHT	20	100	100	100	
Periarteritis nodosa	AST	833	500	125	100	12
	AHT	2500	100	100	<20	20
Collagen disease, type undetermined	AST	250	50			
	AHT	100	20			
Erythema nodosum	AST	1250	833	625	166	125
	AHT	500	500	500	100	100
Henoch-Schönlein's Purpura	AST	2500	333			
	AHT	<20	<20			
Erythema multiforme	AST	12	12			
	AHT	20	20			

* AST—Antistreptolysin O titer in units per cc.
AHT—Antihyaluronidase titer in units per cc.

TABLE 5.—MAXIMUM ANTISTREPTOLYSIN O AND ANTIHYALURONIDASE TITERS IN ACUTE GLOMERULONEPHRITIS AND IN THE NEPHROTIC SYNDROME

Disease	*Antibody**	*Case* 1	2	3	4	5	6	7	8	9	10	11
Acute glomerulonephritis Age less than 14	AST	1250	1250	1250	1250	833	833	833	625	500	250	
	AHT	500	2500	100	2500	2500	2500	500	<20	500	500	
Acute glomerulonephritis Age greater than 14	AST	500	500	250	250	250	166	125				
	AHT	500	500	500	500	500	100	500				
Nephrotic syndrome Age less than 5 years Probable initial glomerulonephritis	AST	12	12	<12	<12							
	AHT	100	<20	<20	<20							
Nephrotic syndrome Age greater than 5 years No initial glomerulonephritis	AST	12	12	<12	<12	<12	<12					
	AHT	20	<20	<20	<20	<20	<20					
Nephrotic syndrome Age 19 to 22 years Probable initial glomerulonephritis	AST	12	12	<12								
	AHT	20	20	<20								
Nephrotic syndrome Age 16 to 50 years No initial glomerulonephritis	AST	50	12	12	<12	<12	<12	<12	<12	<12	<12	<12
	AHT	100	100	<20	100	20	20	<20	<20	<20	<20	<20

* AST—Antistreptolysin O titer in units per cc.
AHT—Antihyaluronidase titer in units per cc.

ronidase titers were also very high (500 units per cc. or more) in 7 of the 8 children. In 1, no measurable antibody was present. The results in 7 adults were not greatly dissimilar but the antistreptolysin titers were not so strikingly elevated, the mean titer being only 292 units per cc. Large amounts of hyaluronidase were present in every instance.

NEPHROTIC SYNDROME. Sera obtained from 24 examples of the nephrotic syndrome were studied (Table 5). The disorder probably followed an acute glomerulonephritis in 7 cases. The onset in the others was insidious. Amyloid disease, multiple myeloma, and intercapillary glomerulosclerosis were excluded, insofar as possible, in every instance. Ten of the subjects were children and 14 were adults. The disease had been present for 1 to 15 months in all but 3 when the sera were collected. The mean duration of illness was about 9 months.

The antistreptolysin O titers were uniformly low regardless of the nature of the onset, the age of the patient, or the duration of the illness. In only 1 case was the level greater than 12 units per cc., and, in 12, less than measurable amounts were present.

Antihyaluronidase was similarly absent or demonstrated in small amounts in 21 cases. Concentrations of 100 units per cc. were discovered in 3. One of these was a child who developed the nephrotic syndrome within a few months after an acute nephritis. The other 2 were adults not clinically different from the other cases.

Discussion. Antistreptolysin O and streptococcal antihyaluronidase are believed to be specific antibodies produced by the contact of enzymatic products of the hemolytic streptococcus with the tissues of the infected human being. They are present in the serum of the newborn infant in amounts approximating those of the mother but disappear rapidly. Concentrations of both are uniformly too small to measure at the sixth month of age.

The subsequent development of these antibodies has been described in previous reports[3,12]. There is a progressive increase in the vigor of antibody production with advancing age through the first years of childhood which may well be associated with conditioning of the antibody forming organs by repeated contact with the hemolytic streptococcus. Streptococcal hyaluronidase appears to be a weaker antigen than streptolysin O.

This paper catalogues the results of the measurement of these 2 antibodies in a large number of healthy persons and in a number of disease states.

Antistreptolysin O reached its peak concentration during late childhood and then declined gradually so that low levels were the rule during the fifth and sixth decades. The highest mean concentrations of antihyaluronidase were also discovered in older children. Only small amounts were present in the sera of many healthy medical students.

A greater proportion of older persons had high or moderately high titers of antihyaluronidase than of antistreptolysin O. The decrease in the mean level of the latter antibody after childhood was relatively much greater (*circa* fourfold) than that of antihyaluronidase (*circa* 1.5-fold).

Many previous investigators have described the presence of large amounts of antistreptolysin O and antihyaluronidase in acute rheumatic fever and similar results were obtained during the present study. Every active case accepted on clinical grounds for inclusion in the group had serum titers of antistreptolysin O of 166 units per cc. or more. Antihyaluronidase concentrations were also high in all but 2 cases.

This antibody was never discovered in measurable quantities in the serum of 1 case. This argues against any essential role of antihyaluronidase in the pathogenesis of rheumatic fever.

Patients with early rheumatoid arthritis fell into 2 groups. The antistreptococcal antibody titers were low to very low in 70% and very high in 30%. Similar results were recorded by others many years ago[1,2]. These observations raise the possibility of infection by the hemolytic streptococcus as a precursor event in certain cases of rheumatoid arthritis. The hazards of immunological study as a differential diagnostic tool are emphasized.

A number of cases of various of the other collagen diseases and related disorders were studied. A probable association in the San Francisco area between most cases of erythema nodosum and infection by the hemolytic streptococcus was demonstrated.

Antistreptolysin levels were high in 2 examples of Henoch-Schönlein's purpura but antihyaluronidase was immeasurably low. This is of interest and should be investigated further. In no other subgroup were streptococcal antibodies consistently elevated or low with the exception of 2 cases of erythema multiforme in which very small amounts of both were present in the sera. It is not possible to exclude infection by the hemolytic streptococcus as of possible pathogenetic importance in certain cases of collagen disease on the basis of these observations.

High concentrations of antistreptolysin and antihyaluronidase were discovered regularly in acute glomerulonephritis as previously noted[7,8]. The mean antistreptolysin O titers were higher when this disease occurred in childhood than in any other situation. In 1 instance no antihyaluronidase was present.

Excessively low antibody levels were encountered at all stages of the nephrotic syndrome as was indicated before by Lyttle[8]. The explanation of this fact is not forthcoming. It may be related to a defect in formation or increased rate of destruction of antibody protein, or to a loss of this substance in the urine. A combination of these factors may play a role.

The measurement of the various hemolytic streptococcal antibodies by many investigators has served to indicate the role of these organisms in the pathogenesis of a number of disorders including rheumatic fever, glomerulonephritis, erythema nodosum, and Henoch-Schönlein's purpura. The use of these techniques for diagnostic purposes in the individual patient is fraught with many difficulties. Most important of these is the very frequent occurrence of high titers of these antibodies in the sera of healthy children from 5 to 12 years of age. Most of the diseases in which these studies are applicable have their highest incidence in this age group.

Very low titers (50 units or less per cc.), especially of antistreptolysin O, in the serum of the patient strongly suggests that 1 of these poststreptococcal disorders is not present. Elevated antibody levels will rarely be of conclusive diagnostic assistance. Concentrations of antistreptolysin or of antihyaluronidase of 500 units or more per cc. will rarely be discovered in individuals who have not had a hemolytic streptococcal infection within the recent past. This information is often helpful in building a complete picture of the sequence of events in certain clinical situations.

Summary. The serum antistreptolysin O and streptococcal antihyaluronidase titers were measured in a large number of healthy persons and in sev-

eral disease states. The antibody levels rose to a peak in late childhood and then declined. Large amounts of 1 or both were present in early active rheumatic fever, erythema nodosum, acute glomerulonephritis, Henoch-Schönlein's purpura, and certain cases of rheumatoid arthritis and periarteritis nodosa. Excessively low concentrations were invariably present in the serum of patients exhibiting the nephrotic syndrome.

REFERENCES

1. **Blair, J. E.**, and **Hallman, F. A.**: J. Clin. Invest., **14**, 505, 1935.
2. **Dawson, M. H.**, and **Olmstead, M.**: Proc. Soc. Exper. Biol. & Med., **34**, 82, 1936.
3. **Di Caprio, J. M., Rantz, L. A.**, and **Randall, E.**: Arch. Int. Med. (In Press).
4. **Earle, D. P., Loeb, E. N., Seegal, D., Lyttle, J. D.**, and **Jost, E. L.**: J. Clin. Invest., **21**, 483, 1942.
5. **Friou, G. J.**, and **Wenner, H. A.**: J. Infect. Dis., **80**, 185, 1947.
6. **Harris, T. N.**, and **Harris, S.**: Am. J. Med. Sci., **217**, 174, 1949.
7. **Harris, T. N., Harris, S., Dannenberg, A. M.**, and **Hollander, J. L.**: Ann. Int. Med., **32**, 917, 1950.
8. **Lyttle, J. D., Seegal, D., Loeb, E. N.**, and **Jost, E. L.**: J. Clin. Invest., **17**, 631, 1938.
9. **Quinn, R. W.**: J. Clin. Invest., **27**, 463, 1948.
10. **Rantz, L. A., Randall, E.**, and **Rantz, H. H.**: Am. J. Med., **5**, 3, 1948.
11. **Rantz, L. A.**, and **Randall, E.**: Proc. Soc. Exper. Biol. & Med., **59**, 22, 1945.
12. **Rantz, L. A., Maroney, M.**, and **Di Caprio, J. M.**: Arch. Int. Med., **87**, 360, 1951.

THE EFFECT OF L-CYSTEINE ON NITROGEN MUSTARD THERAPY*†

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Nitrogen mustard (HN2) has an injurious effect on normal hematopoietic tissue as well as on certain neoplastic tissue. However, the lack of selective effect for neoplastic tissue limits the amount which can be used in therapy since large or repeated doses may produce a severe depression of the bone marrow with development of anemia, leukopenia and thrombocytopenia, often associated with hemorrhagic manifestations. Although the margin of safety is small, it is reported that the maximum effect on neoplastic tissue is produced by giving the largest doses of HN2 that can be tolerated without toxic complications[3]. Presumably, then, it would be desirable to obtain a method for protection of the normal hematopoietic tissue without affecting the injurious effect of HN2 on neoplastic tissue.

Administration of L-cysteine to rabbits prior to the injection of HN2 greatly diminishes the severe leukopenia which is regularly induced by HN2[7]. This apparent protection occurs only if L-cysteine is administered prior to the HN2 and does not occur if it is injected immediately after the HN2. A study of some of the structural requirements of compounds which prevent this leukopenia indicates that the presence in the molecule of reactive sulfhydryl, amino and carboxyl groups in close proximity is essential[8]. Certain other compounds with chemical structures similar to that of cysteine exert no protective effect if the specific structural arrangement is modified or is not present in the molecule. Since these compounds are highly reactive with HN2 *in vitro* but do not prevent leukopenia *in vivo*, it is unlikely that the effect of L-cysteine results merely from chemical inactivation of HN2. The effect of L-cysteine in modifying the neutropenia in animals which are exposed to large amounts of irradiation[5] is further evidence that L-cysteine may protect against leukopenia in a specific manner. Accordingly, the protective effect of L-cysteine on HN2-induced leukopenia was studied in relation to the therapeutic effect of HN2 in patients with neoplastic diseases.

Methods. L-cysteine hydrochloride‡ was given intravenously to 30 patients and orally to 4 patients with various neoplastic diseases (Tables 1 and 2) prior to the administration

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of HN2* [methyl bis (beta chlorethyl) amine hydrochloride]. For intravenous administration, L-cysteine hydrochloride was prepared as a 20% solution in distilled water. The pH was adjusted to 7.0 by the addition of approximately 1.0 cc. of 30% sodium hydroxide for each 5.0 cc. of 20% cysteine solution. The neutralized solution was sterilized by Seitz filtration, mixed with 1000 cc. of 5% glucose in water, and was administered intravenously by a slow drip over a period of 2 to 4 hours. The amount of L-cysteine hydrochloride administered varied from 10 to 30 gm. prior to each dose of HN2, the usual dose being 15 to 20 gm. The patients receiving oral therapy were given 10 to 15 gm. of powdered L-cysteine hydrochloride in capsules swallowed with milk.

Immediately after the intravenous administration of L-cysteine, or 1 hour after oral administration, a freshly prepared saline solution of HN2 containing 1 mg. per cc. was injected intravenously. Seventeen patients received a total of 0.4 mg. per kg., usually divided in 2 consecutive daily doses (Table 1). Seventeen patients 0.8 to 1.5 mg. per kg., usually divided in 2 consecutive daily doses (Table 2).

Leukocyte and differential counts were performed daily during the next 14 or more days. The erythrocyte count, hemoglobin content and hematocrit were determined at intervals of 1 week. The platelet count was determined once a week in 24 patients and changes in the number of platelets were estimated by inspection of cover slip films in the remainder. The maximal fall in the total leukocyte and polymorphonuclear count was calculated as percent of the initial count.* The percent of fall occurring in patients receiving combined cysteine and HN2 therapy was compared with that occurring in 25 patients with similar clinical conditions who had received a total of 0.4 mg. HN2 per kg. without cysteine.

The clinical status was evaluated by fol-

TABLE 1.—THE EFFECT OF L-CYSTEINE ON THE LEUKOPENIA INDUCED BY USUAL DOSES OF NITROGEN MUSTARD

Case	*Diagnosis*	*HN2 (mg./kg.)*	*L-Cysteine HCL (gm.)*	*Max. fall in WBC's (% of initial count)*	*Max. fall in PMN's (% of initial count)*	*Thrombocytopenia*	*Remarks*
1	Hodgkin's	0.1 × 4	15 × 4	51	43	None	Regression of nodes. Disappearance of fever.
2	Hodgkin's	0.2 × 2	20 × 2	36	42	None	Decrease in pleural effusion.
3	Hodgkin's	0.5 × 1	15 × 1	69	72	None	Advanced stage of disease.
4	Hodgkin's	0.2 × 2	15 × 2*	36	31	None	Oral cysteine administered.
5	Hodgkin's	0.2 × 2	15 × 2	69	70	None	Terminal case. Bone marrow involved.
6	Hodgkin's	0.2 × 2	15 × 2*	55	55	None	Oral cysteine, excellent response
7	Mycosis fungoides	0.2 × 2	15 × 2	54	63	Slight	Terminal
8	Acute monocytic leukemia	0.2 × 2	15 × 2	57	26	†	Developed Tbc. Recovered. Still living after 8 months.
9	Acute monocytic leukemia	0.2 × 2	20 × 2	82	61	†	Excellent but very temporary improvement.
10	Acute monocytic leukemia	0.2 × 2	20 × 2	44	29	†	Excellent but very temporary improvement.
11	Acute monocytic leukemia	0.2 × 2	15 × 2	54	56	†	Excellent but very temporary improvement.
12	Leukosarcoma	0.2 × 2	15 × 2	68	59	†	Decrease in pleural effusion.
13	Leukosarcoma	0.2 × 2	15 × 2	72	43	†	Good temporary improvement.
14	Neuroblastoma	0.4 × 1	15 × 1	49	47	Slight	Dramatic regression of tumor masses. Improvement in RBC's.
15	Neuroblastoma	0.4 × 1	10 × 1*	32	23	None	Oral cysteine administered.
16	Adenocarcinoma lung	0.2 × 2	15 × 2	30	26	None	Only slight improvement.
17	Carcinoma, esophagus	0.2 × 2	15 × 2	30	46	Slight	Administered prior to surgery

* L-Cysteine hydrochloride administered orally.
† Thrombocytopenia was present before nitrogen mustard was administered.

$$\text{* Percent fall} = \frac{\text{Initial count} - \text{lowest count} \times 100}{\text{Initial count}}$$

lowing changes in the temperature, body weight, size of tumor masses as determined by clinical inspection and serial Roentgen-ray examinations, as well as by subjective changes of appetite, strength and well being.

Results. The severe nausea and vomiting which characteristically accompanies the injection of HN2 was reduced in most patients receiving with neoplastic conditions receiving 0.1 mg. HN2 per kg. for 4 doses without prior administration of cysteine, the fall in the total leukocyte count averaged 79% of the initial counts and the fall in the polymorphonuclear leukocytes averaged 82% of the initial counts. When L-cysteine was administered to patients prior to the injection of the same total dose of HN2, the fall in the total leukocyte count averaged 52% of the initial counts and the fall in polymorphonuclear leukocytes averaged 45% of the initial counts. Administration of 10 to 30 gm. of L-cysteine prior to the injection of 0.8 to 1.5 mg. of HN2 per kg. (total dose) did not prevent the development of a severe leukopenia, the average fall in the total leukocyte and polymorphonuclear counts being 83 and 86% respectively of the initial counts. In the 4 patients studied, oral administration of L-cysteine was as effective as intravenous administration in cysteine and was occasionally entirely absent. Too rapid intravenous administration of cysteine resulted in nausea and vomiting which could be diminished, but not always entirely eliminated, by decreasing the rate of administration. Nausea and vomiting rarely occurred following oral administration of cysteine in gelatin capsules. No other toxic manifestations were observed.

TABLE 2.—THE EFFECT OF L-CYSTEINE ON THE LEUKOPENIA INDUCED BY LARGE DOSES OF NITROGEN MUSTARD

Case	*Diagnosis*	*HN2 (mg./kg.)*	*L-Cysteine HCL (gm.)*	*Max. fall in WBC's (% of initial count)*	*Max. fall in PMN's (% of initial count)*	*Thrombocytopenia*	*Remarks*
1	Bronchogenic carcinoma	0.5 × 2	20 × 2	90	96	Moderate	No improvement.
2*	Bronchogenic carcinoma	0.4 × 2	20 × 2	73	89	None	Dramatic improvement.
3*	Bronchogenic carcinoma	0.5 × 2	20 × 2	90	97	None	Dramatic improvement. Regression of brain metastases.
4	Bronchogenic carcinoma	0.5 × 3	15 × 3	91	91	Marked	Slight temporary improvement
5	Bronchogenic carcinoma	0.5 × 2	15 × 2	71	91	Moderate	Relief of pain.
6	Bronchogenic carcinoma	1.0 × 1	20 × 1	80	84	Moderate	Relief of pain.
7*	Bronchogenic carcinoma	0.4 × 2	30 × 2	69	70	None	Dramatic improvement.
8*	Bronchogenic carcinoma	0.5 × 2	20 × 2	86	85	Moderate	Dramatic improvement. Regression in metastatic lesions.
9	Bronchogenic carcinoma	0.5 × 2	20 × 2	86	87	Moderate	Relief of pain.
10	Bronchogenic carcinoma	1.0 × 1	20 × 1	91	96	Moderate	No improvement.
11	Bronchogenic carcinoma	0.5 × 2	20 × 1	93	95	Marked	No improvement.
12*	Bronchogenic carcinoma	0.4 × 2	10 × 2†	84	90	Moderate	Moderate improvement.
13	Breast carcinoma	0.5 × 2	15 × 2	88	90	Moderate	No improvement.
14	Malignant thymoma	0.5 × 2	20 × 1	92	94	Marked	Moderate improvement.
15	Leukosarcoma	0.4 × 2	15 × 2	50	21	None	Dramatic improvement.
16	Reticulum cell sarcoma	1.0 × 1	20 × 1	93	97	Marked	Moderate improvement.
17	Hodgkin's	0.4 × 2	15 × 2	80	91	None	Far advanced. Moderate improvement.

* Small cell bronchogenic carcinomas.
† L-Cysteine hydrochloride administered orally.

EFFECT OF L-CYSTEINE ON LEUKOPENIA AND THROMBOCYTOPENIA. The changes in the leukocyte count when L-cysteine was given before HN2 are summarized in Table 3. In 25 patients

modifying the degree of leukopenia developing after the injection of HN2.

By comparison, the administration of 300 to 500 mg. of L-cysteine per kg. to rabbits prior to the injection of 2.5 mg. of HN2 per kg. resulted in an average fall in the total leukocytes of 38% of the initial counts and an average fall in the polymorphonuclear cells of 32% of the initial counts. Injection of the same amount of HN2 to rabbits without administering L-cysteine beforehand resulted in a fall in the leukocyte and polymorphonuclear counts of 84 and 81% respectively of the initial counts (Table 3).

CLINICAL RESPONSE IN PATIENTS RECEIVING L-CYSTEINE PRIOR TO 0.4 MG. HN2 PER KG. Prior administration of L-cysteine did not appear to modify the clinical effects which would have been expected from the HN2. Disappearance of fever, decrease in size of lymph nodes, decrease in pleural effusions, improvement in appetite, strength and sense of well being were noted in 5 of the 6 patients with Hodgkin's disease. Striking clinical changes of improvement occurred even in those patients who developed only a moderate leukopenia (Fig. 1). No significant improvement was observed in patients

TABLE 3.—EFFECT OF L-CYSTEINE ON MUSTARD-INDUCED LEUKOPENIA

	Average Maximum Fall in WBC's (% of initial count)	*Average Maximum Fall in PMN's (% of initial count)*
Nitrogen Mustard 2.5 mg./kg. in Rabbits	84	81
L-Cysteine Administered before 2.5 mg. HN2 per kg. in Rabbits	38	32
Nitrogen Mustard 0.4 mg./kg. in Humans	79	82
L-Cysteine Administered prior to 0.4 mg. HN2 per kg. in Humans	52	45
L-Cysteine Administered prior to 0.8–1.5 mg. HN2 per kg. in Humans	83	86

In patients receiving a total of 0.4 mg. HN2 per kg. after the administration of L-cysteine, no appreciable fall in platelets occurred in 8 patients and a slight thrombocytopenia developed in 3. In the others a severe thrombocytopenia was present as a result of the disease state before therapy was instituted. There was no significant decrease in platelets in 3 patients receiving 0.8 to 1.5 mg. HN2 per kg. A moderate thrombocytopenia developed in 9 and a marked thrombocytopenia in 5. Recovery to normal levels was rapid in those patients who developed thrombocytopenia.

5 and 7, (Table 1). These patients had terminal illnesses of Hodgkin's disease and mycosis fungoides, respectively.

In the 4 patients with acute monocytic leukemia who were treated with L-cysteine and HN2 there appeared to be a temporary remission of short duration as evidenced by an increase in the sense of well-being, in appetite and in strength in each patient. Relatively good protection of the polymorphonuclear leukocytes with marked depression in the number of circulating immature monocytes occurred (Figs. 2 and 3). A similar striking protection of neutrophils and disappearance of

the abnormal mononuclear cells occurred in 1 of the patients with lympholeukosarcoma (Patient 13, Table 1, Fig. 4). This patient and 1 of the patients with monocytic leukemia (Fig. 2) were treated with additional HN2 without cysteine. No further clinical improvement was noted and a rapid fall in neutrophils occurred.

of the lung and in 1 patient with squamous cell carcinoma of the esophagus (Patients 16 and 17, Table 1).

CLINICAL RESPONSE IN PATIENTS RECEIVING L-CYSTEINE PRIOR TO 0.8 TO 1.5 MG. HN2 PER KG. Twelve patients with carcinoma of the lung were given L-cysteine followed by the injection of a total of 0.8 to 1.5 mg. HN2 per kg.

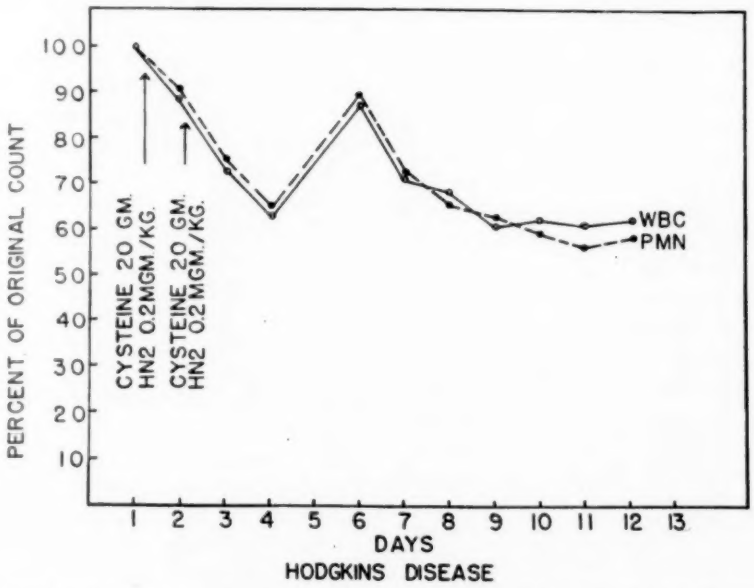

FIG. 1. Combined cysteine and mustard therapy in a patient with Hodgkins disease. Fever disappeared, lymph nodes became smaller, reaccumulation of pleural effusion ceased and the patient's appetite, strength and sense of well-being improved. This beneficial effect was obtained despite a relatively small decrease in the leukocyte count.

One patient with neuroblastoma was treated twice (Patient 14 and 15, Table 1). There was rapid regression of the tumor masses, disappearance of ascites and edema, return of the erythrocyte count to normal, and increase in strength, appetite and well-being. These beneficial changes were achieved with relatively good protection of the leukocyte count and persisted for 1 month on each occasion.

There was no significant improvement in 1 patient with adenocarcinoma

Seven of the 12 had either squamous cell or adenocarcinoma and 5 patients had small cell carcinoma of the lung. Patients with either squamous cell or adenocarcinoma of the lung had little subjective and no objective improvement. However, pain resulting from bone involvement was relieved in 3 of these patients. Two patients had pathologic fractures of lumbar vertebrae and had required repeated large doses of opiates. Following therapy there was marked reduction in the requirements

for opiates. The significance of these subjective changes is difficult to evaluate.

Four of the 5 patients with small cell carcinoma of the lung experienced rapid objective improvement following therapy (Patients 2, 3, 7 and 8; Table 2). There was rapid regression of hepatomegaly and jaundice due to metastases, improvement in neurologic signs due to cerebral metastases, and reduction in venous pressure due to mediastinal compression. There was also improvement in appetite, strength and sense of well-being. The fifth patient (Patient 12, Table 2) had excellent subjective improvement with reduction in size of the lung lesion but without discernible decrease in the extent of the metastatic lesion in the liver.

A good remission was obtained in a patient with lympholeukosarcoma (Patient 15, Table 2). This patient had previously been treated with L-cysteine and 0.4 mg. HN2 per kg. (Patient 13, Table 1) with a good but temporary improvement. Following a second course of therapy with L-cysteine and 0.8 mg. HN2 per kg. (Patient 15, Table 2) there was further improvement with decrease in size of lymph nodes, marked reduction in the number of circulating abnormal mononuclear cells and gain in weight and strength. Despite the remarkable clinical improvement and the large dose of HN2 employed, the fall in total leukocyte count was only 50% of the control count and the fall in the neutrophils was only 21% of the control count. During the course of therapy he developed pulmonary tuberculosis which was arrested with streptomycin therapy and bed rest. He is still alive and doing well 12 months after therapy was discontinued, with very little evidence for the presence of lympholeukosarcoma and no evidence of active tuberculosis.

In 1 patient with reticulum cell sarcoma (Patient 16, Table 2), which had not responded to irradiation, there was significant regression in the tumor mass and general clinical improvement following treatment with 1.0 mg. HN2 per kg. Relapse occurred within 4 weeks after therapy, however. The patients with breast carcinoma, malignant thymoma and terminal Hodgkin's disease had no discernible improvement.

Discussion. Administration of L-cysteine prior to HN2 resulted in a definite and frequently striking decrease in the leukopenia regularly induced by HN2. The protective effect was not as great nor as consistent as that occurring in healthy rabbits (Table 3). This may be attributed in part to involvement of the bone marrow and depletion of hematopoietic tissue by neoplastic disease and in many instances to bone marrow damage induced by prior radiation therapy. The sensitivity of human leukocytes to HN2 compared with rabbit leukocytes may also be a factor in the degree of protection attained. Thus, approximately 5 to 6 times as much HN2 per kg. of body weight is required to produce leukopenia in rabbits as in humans. Despite this species difference, approximately the same amount of L-cysteine (300 mg. per kg. of body weight) was capable of modifying the leukopenia both in rabbits and man.

Patients treated with 0.4 mg. HN2 per kg. without cysteine occasionally develop only a moderate leukopenia. This was an infrequent occurrence in the control group of 25 patients, most of whom developed a severe leukopenia. It is difficult to compare the degree of leukopenia obtained in this study with that reported in the literature when HN2 is administered without cysteine. In most instances it is stated that the leukocyte count falls to 1000 to 3000 cells/c.mm. without

stating the initial count[3,4,6]. However, the occurrence of leukocyte counts below 1000 per c.mm. with HN2 therapy is not infrequent and the development of severe leukopenia is a common observation. Statistical analysis reveals a significant difference between the decrease in leukocytes in those patients treated with both drugs as compared with those patients treated with HN2 alone.*

The presence of leukopenia usually requires that HN2 therapy be given cautiously, if at all. With prior administration of L-cysteine, however, the usual doses of HN2 (up to a total of 0.5 mg. per kg.) were given without untoward effects in the presence of pre-existing leukopenia.

The difference in response of various types of leukocytes to HN2 when cysteine is administered beforehand is apparent. Of the normal cells, a slightly greater protection of neutrophils than of lymphocytes was obtained. It has been demonstrated[2] that lymphocytes are similarly more sensitive to radiation than are the granulocytes. The variable effect of L-cysteine on cellular sensitivity to HN2 was especially notable in patients with acute monocytic leukemia and lympholeukosarcoma. The abnormal cells almost disappeared from the blood and bone marrow following combined therapy with L-cysteine and HN2, while there was only a minor decrease of the granulocytes. In these cases, therefore, L-

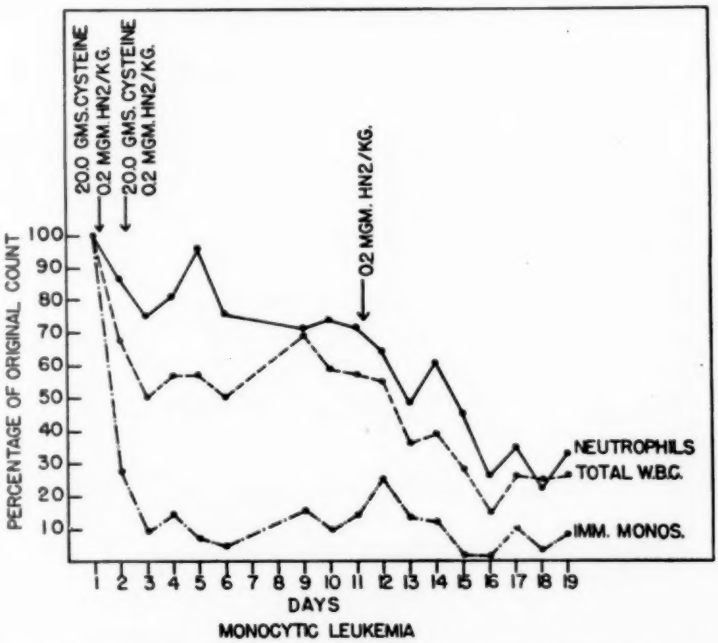

FIG. 2. Effect of combined cysteine and mustard therapy on the leukocyte count in acute monocytic leukemia. There was a marked decrease in the immature monocytes with good protection of the neutrophils. Injection of mustard without cysteine resulted in a prompt fall in neutrophils.

* We are indebted to Dr. George Badger for the statistical analysis.

cysteine afforded more protection from HN2 to the normal granulocytic than to the leukemic elements.

In neoplastic diseases not associated with the presence of abnormal cells in the blood and marrow, evaluation of therapeutic results is admittedly more difficult. Careful observation leads us to believe, however, that despite the prevention of severe leukopenia, apparently maximum clinical improvement occurred as measured both by objective and subjective findings in the patients. Thus, there was disappearance of fever, decrease in size of tumor masses, and improvement in appetite and well-being, even when administration of L-cysteine had afforded good protection of the leukocytes. Subsequent therapy with HN2 alone in a few cases did not result in further clinical improvement although the expected severe leukopenia occurred promptly. The production of leukopenia has been advocated as an index of adequate HN2 therapy. This criterion is not valid when L-cysteine is administered beforehand.

The mechanism of the apparent selective protection of granulocytes is not known. The fact that abnormal cells are not protected to as great a degree, if at all, and the observation that L-cysteine similarly modifies the leukopenia resulting from Roentgen-irradiation makes it evident that the leukocyte protection is not achieved by direct partial or complete inactivation of HN2 by L-cysteine. It may be postulated that leukopenia induced by HN2 or Roentgen-irradiation results from inactivation or destruction of some substance or substances necessary for normal leukocyte metabolism and that L-cysteine exerts a sparing or protective effect by competition with HN2

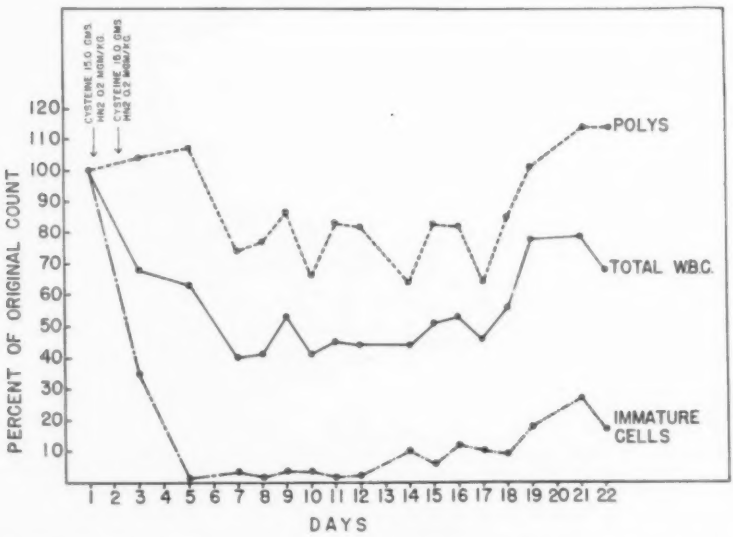

FIG. 1. Combined cysteine and mustard therapy in a patient with Hodgkin's disease. Fever monocytic leukemia. The moderate decrease in the total leukocyte count was due primarily to the decrease in immature monocytes. The relatively slight change in the neutrophil count compared to that of the immature monocytes is striking.

for the substance(s). The lack of protective effect when L-cysteine is given after HN2 or Roentgen-irradiation administration, even immediately, indicates that destruction of L-cysteine itself is not a factor. These and previous observations[2] suggest further that L-cysteine and closely related compounds containing sulfhydryl, amino and carboxyl groups in close apposition may normally have a role in leukocyte metabolism, although definite proof of this is lacking at this time.

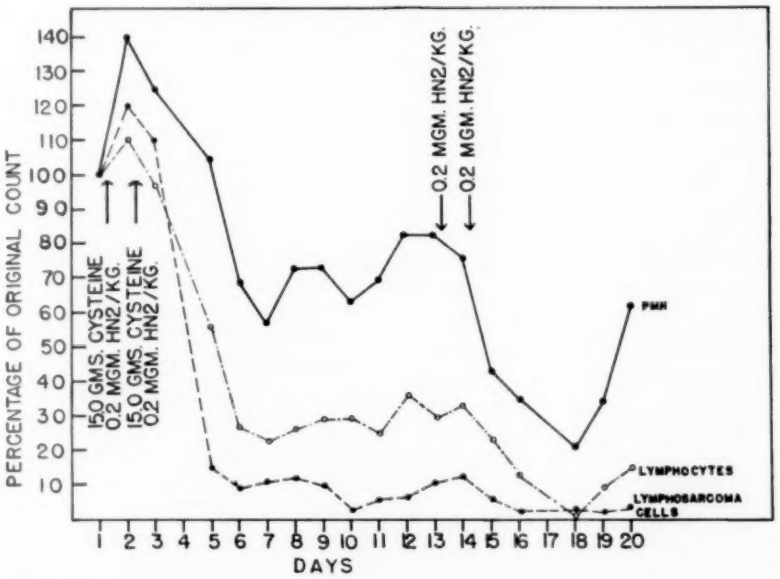

FIG. 4. Effect of combined cysteine and mustard therapy on the leukocyte count in lympholeukosarcoma. The relatively good protection of neutrophils is striking. Administration of mustard without cysteine results in the prompt development of neutropenia.

The combined use of L-cysteine and HN2 permitted the administration of up to 1.5 mg. of HN2 per kg. of body weight without the occurrence of appreciably greater leukopenia or thrombocytopenia than was usually encountered with the customary smaller doses (0.4 mg. HN2 per kg. body weight) given without L-cysteine. No significant therapeutic effect was obtained with the use of the large doses in disease conditions which did not ordinarily respond to smaller doses. Certain neoplastic conditions are not susceptible to HN2 therapy and the use of very large doses did not overcome this lack of response in the conditions studied and in the dose range used. Thus, there was no regression of tumor masses or alteration of the course in patients with adenocarcinoma or squamous cell carcinoma of the lung, terminal cases of Hodgkin's disease and in radio-resistant reticulum cell sarcoma. Significant relief of pain did occur in the patients with metastatic bone lesions due to adenocarcinoma and squamous cell carcinoma of the lung.

The use of large doses of HN2 resulted in measurable improvement in the patients with small cell carcinoma of the lung and in 1 patient with lympholeukosarcoma. It cannot be

stated definitely that the amount of benefit derived was any greater than that which might have been obtained with the customary dosage. Further therapeutic trial is indicated to determine whether large doses are more effective than the more customary doses in conditions usually responding to HN2 therapy.

Within the dose range used, larger amounts of L-cysteine did not afford greater leukocyte protection. About the same degree of protection was afforded by 10 gm. as by 30 gm. given intravenously before each injection of HN2. However, since 2 to 4 hours were required to administer the material intravenously, it is possible that much of the L-cysteine might have been excreted or metabolized before the HN2 was administered. Determinations of the blood free-sulfhydryl level[1] in 5 patients following cysteine administration have not shown any significant increase in sulfhydryl concentration. This may be due to rapid removal from the blood stream with prompt tissue or cellular saturation.

Oral administration of L-cysteine was used because of its simplicity and because it was thought that administration of a single large oral dose might result in higher blood levels than could be obtained with the slower intravenous administration. There is no question that orally-administered L-cysteine was effective, although in the few cases studied there was no significant change in blood sulfhydryl levels. At the present time, powdered L-cysteine HCL is being given in capsules in doses of 10 to 15 gm. 1 hour prior to administration of HN2. Preliminary results indicate satisfactory modification of leukopenia as well as considerable reduction in the nausea and vomiting associated with HN2 therapy. The ease with which L-cysteine may be administered in this manner makes it readily adaptable for routine use. The use of larger doses is complicated by the acidity of L-cysteine hydrochloride while neutralized solutions are excessively hypertonic. Use of other salts might obviate these difficulties, making oral administration of larger doses possible if it proves to be desirable.

The cellular effects of HN2 and irradiation are known to be similar. The parenteral administration of L-cysteine has been shown to modify the leukopenia induced by either HN2 or irradiation in animals[5,8]. Since oral L-cysteine modifies HN2-induced leukopenia in humans without any apparent modification of the beneficial therapeutic effects, it may similarly be effective in radiation therapy. The effect of oral-L-cysteine on the beneficial aspects of radiation therapy as well as on the leukopenia induced by irradiation is therefore investigated.

The results strongly suggest that administration of L-cysteine prior to the injection of HN2 affords selective protection of granulocytes or granulocyte precursors without providing the same protection to malignant cells. The difficulties in establishing beyond doubt the differences between degrees of protection of various normal and malignant cells are recognized so that further experimental evidence as well as prolonged clinical observation are necessary. Results obtained thus far, however, indicate that the prior administration of L-cysteine offers some practical benefit in the use of HN2 therapy.

Summary. The administration of L-cysteine prior to the injection of nitrogen mustard (HN2) decreases and modifies the severe leukopenia and thrombocytopenia usually induced by HN2. In addition L-cysteine causes reduction in the nausea and vomiting which occurs following the injection of HN2.

Despite the modification of leukopenia when L-cysteine is administered prior to HN2, there is no apparent diminution of the beneficial therapeutic effects of HN2 in the therapy of various malignant diseases. The results suggest that there is a selective protective effect on granulocytes without protection of malignant cells. Further clinical and experimental study is necessary to establish this beyond doubt.

The mechanism by which L-cysteine modifies HN2-induced leukopenia is not known. It is suggested that L-cysteine and related compounds may have a role in leukopoiesis.

The combined use of L-cysteine and HN2 permits the administration of large doses of HN2 without inducing any greater leukopenia or thrombocytopenia than is usually encountered with customary amounts of HN2. The use of large doses of HN2 has not resulted in significant benefit in any group of diseases not usually benefited by HN2 therapy. The extent to which large doses of HN2 benefits cases ordinarily susceptible to HN2 therapy requires further study.

The results obtained thus far indicate that administration of L-cysteine prior to HN2 therapy offers some practical benefit.

REFERENCES

1. **Barron, E. S. G.**, and **Flood, V.**: Argonne National Laboratory Reports, 4163, p. 116.
2. **Jacobson, L. O., Marks, E. W.**, and **Lorenz, E.**: Radiology, **52**, 371, 1949.
3. **Karnofsky, D. A.**: Advances in Internal Medicine, Volume IV. Chicago, Illinois: Year Book Publishers, Inc., 1950.
4. **Karnofsky, D. A., Craver, L. F., Rhoads, C. P.**, and **Abels, J. C.**: Approaches to Tumor Chemotherapy. Washington, D. C., Am. Assn. Advancement Sci., p. 319, 1947.
5. **Rosenthal, R. L., Goldschmidt, L.**, and **Pickering, B. I.**: Am. J. Physiol., **166**, 15, 1951.
6. **Spurr, C. L., Jacobson, L. O., Smith, R. T.**, and **Barron, E. S. G.**: Approaches to Tumor Chemotherapy. Washington, D. C., Am. Assn. Advancement Sci., p. 306, 1947.
7. **Weisberger, A. S.**, and **Heinle, R. W.**: J. Lab. & Clin. Med., **36**, 872, 1950.
8. **Weisberger, A. S., Heinle, R. W.**, and **Levine, B.**: J. Clin. Invest., in press.

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DIETARY CHOLESTEROL AND ATHEROSCLEROSIS

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Presented in Philadelphia at the December 31, 1951 meeting of the American Association for the Advancement of Science.

THE current interest in the role of dietary cholesterol in the pathogenesis of arteriosclerosis has been markedly increased by the reports of Gofman[25,26] implicating certain cholesterol containing lipoprotein molecules in the atherosclerotic process. Recently, such tremendous emphasis has been placed on the value of low fat, low cholesterol diets in retarding the progress of atherosclerosis[18,27] that in some metabolic circles a man is looked on with considerable suspicion if he is so foolhardy as to appear to enjoy eating eggs, butter, cheese or other cholesterol-containing foods[19].

There can be no doubt that cholesterol plays a major role in the development of atherosclerosis. Leary in 1941 in summarizing many years interest in this field indicated that the association between cholesterol and atherosclerosis fulfills Koch's postulates:

1. Excess cholesterol is always present in the active stages of human atherosclerosis.
2. Cholesterol can be identified and extracted from human lesions.
3. Atherosclerosis can be reproduced in animals more exactly than can many human infections in susceptible animals.
4. Cholesterol can be identified and extracted from these experimental lesions.

Perhaps because of the now incontrovertible evidence presented by numerous investigators over many years demonstrating the relationship between cholesterol and atherosclerosis, many clinicians and not a few investigators have been beguiled into placing similar significance, so far as the development of arteriosclerosis is concerned, on the words "cholesterol" and "dietary cholesterol." The demonstration initially by Bloch and Rittenberg[8] and later by Gould[28] and Brady and Gurin[11] that the body synthesized cholesterol from as small radicles as acetate derived from non-cholesterol containing food stuffs, effectively indicated that so far as the body is concerned, the blood and tissue cholesterols may have as their ultimate source non-cholesterol containing foods from the diet. The observations of Chaikoff *et al.*[14] provide additional weight to this concept by demonstrating that atherosclerosis may develop in birds on a diet totally devoid of cholesterol and, indeed, the cholesterol may actually be synthesized within the artery itself[59].

The tabulation of Rosenthal[57] in 1934 indicated that races customarily eating high fat diets had an increased incidence of atherosclerosis and Eskimos and Japanese, with supposedly a low fat intake had less. Snapper[60] also commented on the low incidence of this finding in Chinese. Recently, Steiner[66] noted the low incidence of atherosclerosis in Okinawans, and Cullumbine[16] in the Ceylonese. These

findings must be accepted with some reservation as the life expectancy and general nutritional state of all these groups is very significantly lower than the average in this country. Cullumbine noted that in 1946 the life expectation of a Ceylonese male was 44 years.

Wilens[69] in examining 395 obese persons, 372 of average nutrition and 483 poorly nourished individuals at necropsy found almost twice as many of the poorly nourished group to be essentially free of atherosclerosis as the obese group. This report also indicated that in non-hypertensive persons under 65 years of age there was no significant difference in the occurrence of atherosclerosis in those of average nutrition compared to the poorly nourished group. Similarly Garn, Gertler, Levine and White[23] in studying 97 men who had experienced a myocardial infarct prior to age 40 and 146 healthy men of comparable age and occupation failed to find the group with infarction to be more overweight than the controls. Despite this, recent reports[17,31,41] call attention particularly to the decreased incidence of atherosclerotic vascular disease in countries with a low dietary fat intake as a result of wartime restrictions.

Cholesterol Tolerance Tests. Attempts to demonstrate significant differences in the ability of an individual to handle cholesterol have been made for many years. Bing and Heckscher[7] in 1924 noted more than the usual hyperlipemic reaction after the ingestion of fat in diabetics with normal post-absorptive serum lipids. Since that time many workers have attempted to devise acute cholesterol tolerance tests without uniform success[10,13,15,20,21,35,36,42,49,53,67]. Several workers, however, have demonstrated moderate increases in blood cholesterol levels with prolonged cholesterol feeding[9,22]. Okey and Stewart[47] and Steiner and Domanski[65] were able to produce increases in blood cholesterol by feeding large amounts of egg yolk over a period of several weeks. Plotz[50] reported an increased severity of coronary symptoms in patients with coronary disease who were placed on a high fat diet in the course of peptic ulcer therapy. Recently, Messinger, Porosowska and Steele[44] have implicated in egg yolk an as yet unidentified substance which is not cholesterol but which elevates the cholesterol level of human sera.

The present author[46] studied the changes in total serum cholesterol, cholesterol esters, and lipid phosphorus in 35 young pregnant women on an accurately recorded diet from the fifth month of pregnancy to term and in 30 similar women receiving the same diet plus 2 additional grams of cholesterol supplied in fancy chocolate candy. This quantity of cholesterol is approximately equivalent to the cholesterol contained in 2 eggs, plus 4 quarts of milk, plus 8 pats of butter and a pound of fat meat daily[38]. No discernible rise occurred in any of these lipid fractions over that observed in the normally fed group (Table 1). Furthermore, no alteration in the level of S_f 10–20 molecules was induced in these pregnant women by feeding 2 gm. of additional cholesterol.

Low Cholesterol Feeding. In addition to the workers previously cited[18,19,27] several others have been impressed by the blood cholesterol lowering value of a low cholesterol diet[54,61]. Kempner[37] and more recently Starke[62] have been able to lower total cholesterol levels by the anti-hypertensive rice diet. In 79 patients Kempner noted an average fall from 243 to 186 mg. per 100 cc. and Starke was able to lower the total and esterified

cholesterol in 149 of her 154 patients. Morrison[45] and Priddle[52] have also reported lowering of blood cholesterol levels on a low cholesterol intake. Mellinkoff *et al.*[43] provided 2200 to 2400 low fat calories (protein hydrolysate and dextrimaltose) to patients with gastrointestinal tract disease and were able to effect lower blood cholesterol values.

Steiner[63,64] has recently reported an average increase of 54 mg. per 100 cc. in 5 patients with coronary arteriosclerosis given 100 gm. of egg yolk powder daily for 6 weeks. In 20 patients fed from 4 to 26 months on a low cholesterol diet from which butter, egg yolk, cream, and fatty meats were excluded but oleomargarine was permitted, he reports the preliminary results indicate the serum cholesterol to be significantly lower in 13 patients, slightly lower in 6 and unchanged in one. The fluctuations in serum cholesterol levels were also less marked on this regimen.

Many other workers, however, have not been able to produce significant lowering of blood cholesterol levels by even rather drastic dietary restriction of fat. Poindexter and Bruger[51] in 1935 failed to note any alteration in the cholesterol content of the plasma in obese patients placed on sharp fat and caloric restriction. This has been confirmed in children[32] and recently in patients receiving 600 to 800 calorie reducing diets[68]. Brown *et al.*[12] reported 1 subject who was kept on a diet of approximately 2 gm. of fat per day for 6 months without exhibiting any change in the total blood fatty acid or cholesterol.

In studying a kindred of 83 persons in which essential familial hypercholesterolemia was present Wilkinson *et al.*[70] demonstrated no relation between the absolute amount of carbohydrate, fat, protein, and cholesterol in the diet or the percentage of the total calories provided by the various dietary constituents and the level of the total serum cholesterol.

In a comparative analysis of the dietary histories of 139 healthy males and 90 males who developed myocardial infarction prior to the age of 40, Gertler, Garn and White[24] found the average quantity of cholesterol ingested by the healthy group to be 3.88 gm. ± 1.46 and in the myocardial infarction group to be 3.30 gm. ± 1.41. No definite relation was evident between the quantity of cholesterol in-

TABLE 1. SERUM CHOLESTEROL, LIPID PHOSPHORUS AND S_f 10-20 VALUES IN PREGNANT WOMEN ON A NORMAL DIET AND THE SAME DIET SUPPLEMENTED BY 2 GRAMS OF CHOLESTEROL IN FANCY CHOCOLATE CANDY DAILY.

Month of Pregnancy	Average Total Serum Cholesterol mg/100 ml.		Average Serum Chol. Esters mg/100 ml.		Average Serum Lipid Phosphorus mg/100 ml.		Cholesterol/Lipid Phosphorus Ratio		S_f 10-20 mg/100 ml.	
	Normal	Chol. Fed	Normal	Chol. Fed.	Normal	Chol. Fed.				
5	235	202	171	145	12.1	11.4	18.0	16.4		
6	227	214	162	148	13.1	11.6	17.6	18.4	43	53
7	240	192	167	136	13.0	11.1	18.1	18.1	33	46
8	250	224	178	158	13.7	12.0	18.4	19.0	56	46
9	257	223	177	154	14.5	12.5	18.2	18.3	48	34
Post-partum	244	227	170	134	13.6	12.7	18.1	18.1	67	49

gested and the serum cholesterol level.

Keys and co-workers[39] in studying a large number of healthy males on a diet containing either less than 2 or more than 3 gm. of cholesterol per week demonstrated that the blood cholesterol level is independent of the intake over a wide range, but with approximately zero cholesterol intake the blood cholesterol level falls at a rate related to the initial height of the cholesterol level. In 1 of his subjects with hypercholesterolemia, after a sharp fall in serum cholesterol levels on an extremely low fat and cholesterol intake, the addition of cholesterol free vegetable oil to the diet, resulted in a rapid return of the serum cholesterol to its previously high levels. This cholesterol elevating effect of vegetable oils has been noted by other observers both in animals[1] and man[33] and emphasizes the importance of an absolute restriction in total fat and not of cholesterol alone if a lowered serum cholesterol is desired[34].

Hatch and Kendall[30] have recently reported on 35 hospitalized patients with severe essential hypertension maintained for a control period of 4 to 18 weeks upon a salt poor diet. (52 mEq. Na) providing 85 gm. of fat and 1 gm. of cholesterol per day. Following this the basic Kempner rice diet was administered for periods of from 4 to 20 weeks. This diet provided 1800 to 2400 calories with only 30 gm. of protein and 3.4 gm. of lipid material including 0.1 gm. of digitonin precipitable sterol of plant origin. They found this diet produced highly variable effects upon the serum lipid pattern although in no case did the levels on the restricted diet decrease below the normal range. They reported that instead of the decrease in level of S_f 12–20 class particles induced by the conventional low-fat, low cholesterol diet, the rice diet evoked a variable response with substantial increases in S_f 12–20 level in 5 cases, a constant level in 5 and decreases in only 2 patients.

These authors[30] observed the excretion of digitonin precipitable sterols in amounts far in excess of the plant sterol content of the rice diet and but little lower than that of the normal diet. They conclude that this provides proof of continuing endogenous sterol synthesis. The serum patterns and their demonstration of the conversion of the carbohydrate (rice) intake in excess of caloric needs into storage fat as judged by changes in body weight, total body water and post absorptive respiratory quotient changes provide these investigators indirect clinical evidence that the metabolism of all these lipids continues uninterruptedly after the exogenous supplies are cut off. Their findings do not support the view that a reduction in the quantity of circulating lipids can be achieved by substituting other foodstuffs for dietary fat.

Beck, Benedict and Lawrence[6] have recently reported the changes in the blood lipid fractions induced in 8 normal males by 4 weeks on a daily diet supplying approximately 1900 calories with 3 gm. of fat, 70 gm. of protein including supplements and 400 gm. of carbohydrate followed by 2 weeks on a similar 2600 calorie diet except that approximately 90 gm. of fat was supplied as sterol-free vegetable fat. All their subjects lost weight and had a fall in the total serum cholesterol during the period of fat restriction. The phospholipid-cholesterol ratios were also increased possibly due to an increase in serum phosphorus as well as the decrease in cholesterol. The addition of sterol-free vegetable fat to the diet resulted in prompt return of serum cholesterol and phospholipid-cholesterol ratios to pre-treatment

levels. The levels of S_f 10–20 molecules in these subjects fluctuated greatly and showed no correlation with the intake of dietary fat (Table 2). These observers were impressed by the difficulties of providing adequate protein and calories in palatable form on this reduced fat regimen and doubt that a strictly fat free dietary would be either practical or desirable.

Discussion. From the data herein reported there can be no doubt that cholesterol plays a major role in the development of atherosclerosis. There also seems to be no doubt that the body can abundantly synthesize cholesterol and even arterial cholesterol in the absence of an exogenous supply. Indeed it is difficult if not impossible to significantly lower plasma cholesterol values by reducing the dietary intake of cholesterol unless sharp restriction of animal and even sterol-free vegetable fat also occurs.

The suggestion that some accompanying factor in the diet as pyridoxine deficiency[29,55,56], deficient protein intake[5,48,58] or dietary phospholipids[4] or lecithin[3] may qualitatively or quantitatively alter hypercholesterolemia deserve additional exploration. The observations that emotional episodes[40] and corticotropin and cortisone[2] administration produce changes in the serum cholesterol levels also must receive more study.

In attempting to determine the significance of variations in dietary intake on the level of the blood cholesterol, it must be recognized that normally considerable spontaneous variation in blood cholesterol occurs[30,47,49] and that these fluctuations are particularly labile in subjects with clinical evidence of vascular disease[64,65]. To ascribe importance to changes in blood cholesterol induced by alterations in the diet, variations of greater magnitude than those spontaneously occurring must be recognized.

TABLE 2. AVERAGE TOTAL CHOLESTEROL, LIPID PHOSPHORUS AND S_f 10-20 MOLECULES IN 8 ADULT MALES AND A NORMAL FAT RESTRICTED, AND STEROL-FREE VEGETABLE FAT CONTAINING DIET. (FROM DATA SUPPLIED BY BECK, BENEDICT AND LAWRENCE[6], USED BY PERMISSION).

	Normal Control Diet	1900 Cal. Diet (3.0 gm Fat 70 gm. Protein) (30 days)	2600 Cal. (90 gm. Sterol-Free Vegetable Fat) (14 days)
Average Total Cholesterol (mg./100 ml.)	243	204	214
Average lipid phosphorus (mg./100 ml.)	9.0	9.2	9.0
Average S_f 10-20 (mg./100 ml.)	34	48	40

Summary. 1. The well-founded relationship of cholesterol to the pathogenesis of atherosclerosis is accepted.

2. The evidence implicating exogenous dietary cholesterol in this condition is reviewed. The experience of several workers in observing both the acute and chronic effects of cholesterol feeding and cholesterol restriction are noted.

3. It is concluded that neither moderate increases or decreases in dietary cholesterol exert any consistently significant effect upon blood cholesterol levels.

4. The almost complete elimination from the diet of all cholesterol and other lipids including sterol-free vege-

table oils is necessary if significant decreases in blood cholesterol levels are to be achieved.

5. It appears likely that the unpalatability of such a diet together with the feeding problems it would produce, makes the widespread recommendation of such a rigidly restricted diet unwise even in the presence of atherosclerotic disease.

6. It is suggested that perhaps attention to other dietary components, especially protein, may alter the physical state of the circulating cholesterol and influence its relationship to the atherosclerotic process.

REFERENCES

1. **Abelin, I.**: Quoted by Keys[39], Helvet. physiol. acta, **6**, 879, 1948.
2. **Adlersberg, D., Schaefer, L.,** and **Drachman, S. R.**: J. Am. Med. Assn., **144**, 909, 1950.
3. **Adlersberg, D.,** and **Sobotka, H.**: J. Mt. Sinai Hosp., **9**, 955, 1943.
4. **Ahrens, E. H.,** and **Kunkel, H. G.**: J. Exper. Med., **90**, 409, 1949.
5. **Barr, D. P., Russ, E. M.,** and **Eder, H. A.**: Am. J. Med., **11**, 480, 1951.
6. **Beck, L. W., Benedict, J. H.,** and **Lawrence, H. W.**: Personal communication.
7. **Bing, H. J.,** and **Heckscher, H.**: Biochem. Ztschr., **144**, 83, 1924.
8. **Bloch, K.,** and **Rittenberg, D.**: J. Biol. Chem., **145**, 625, 1942.
9. **Bloor, W. R.**: J. Biol. Chem., **95**, 633, 1932.
10. **Blotner, H.**: Arch. Int. Med., **55**, 121, 1935.
11. **Brady, R. O.,** and **Gurin, S.**: J. Biol. Chem., **186**, 461, 1950.
12. **Brown, W. R., Hanson, A. E., McQuarrie, I.,** and **Burr, G. O.**: Proc. Soc. Exper. Biol. & Med., **36**, 281, 1937.
13. **Burns, F. J.**: Rhode Island Med. J., **31**, 103, 1948.
14. **Chaikoff, I. L., Lindsay, S., Lorenz, F.W.,** and **Entenman, C.**: J. Exper. Med., **88**, 373, 1948.
15. **Collen, M. F., De Kruif, D.,** and **Geier, F.**: Permanente Found. Med. Bull., **7, 60**, 1949.
16. **Cullumbine, H.**: Cardiovascular Disease in Ceylon. Trans. 5th Conference on Factors Regulating Blood Pressure. New York, Josiah Macy, Jr. Foundation, 1951, p. 124.
17. **Dedichen, J., Strom, A., Adelslein-Jensen, R.,** and **Closs, K.**: Incidence of Atherosclerotic Disease During War Years. 5th Conference on Factors Regulating Blood Pressure. New York, Josiah Macy, Jr. Foundation, 1951, p. 117.
18. **Dobbin, E. V., Gofman, A. F., Jones, H. C., Lyon, L.,** and **Young, C. B.**, Editors: The Low Fat, Low Cholesterol Diet. Garden City, New York, Doubleday and Co., 1951.
19. **Dock, W.**: Correspondence. J. Am. Med. Assn., **134**, 1197, 1947.
20. **Fatch, E. D.,** and **Gregory, R.**: J. Lab. & Clin. Med., **33**, 12, 1948.
21. **Frohling, W.**: Arch. f. Verdamungskr., **59**, 205, 1936.
22. **Gardner, J. A.,** and **Gainsborough, H.**: Biochem. J., **22**, 1048, 1928.
23. **Garn, S. M., Gertler, M. M., Levine, S. A.,** and **White, P. D.**: Arch. Int. Med., **34**, 1416, 1951.
24. **Gertler, M. M., Garn, S. M.,** and **White, P. D.**: Circulation, **2**, 696, 1950.
25. **Gofman, J. W., Jones, H. B., Lindgren, F. T., Lyon, T. P., Elliott, H. A.,** and **Strisower, B.**: Circulation, **2**, 161, 1950.
26. **Gofman, J. W., Lindgren, F., Elliott, H., Mantz, W., Hewitt, J., Strisower, B., Herring, V.,** and **Lyon, T. P.**: Science, **111**, 166, 1950.
27. **Gofman, J. W., Lindgren, F. T., Jones, H. B., Lyon, T. P.,** and **Strisower, B.**: J. Geront., **6**, 105, 1951.
28. **Gould, R. G.**: Circulation, **2**, 467, 1950.
29. **Greenberg, L. D.,** and **Rhinehart, J. F.**: Proc. Soc. Exper. Biol. & Med., **76**, 580, 1951.
30. **Hatch, F. T.,** and **Kendall, F. E.**: Effect of a Cholesterol Free, Low-Fat Diet upon the Serum Lipids in Patients with Essential Hypertension. Presented at the Nov. 5, 1951 meeting of the American Society for the Study of Arteriosclerosis.
31. **Henschen, F.**: J. Geront., **6**, 102, 1951.
32. **Heymann, W.,** and **Rock, F.**: Am. J. Dis. Child., **65**, 235, 1943.
33. **Hildreth, E. A., Hildreth, D. M.,** and **Mellinkoff, S. M.**: Circulation, **4**, 899, 1951.
34. **Hildreth, E. A., Mellinkoff, S. M., Blair, G. W.,** and **Hildreth, D. M.**: Am. J. Med. Sci., **221**, 354, 1951.

35. **Hirsch, E. F.,** and **Carbonaro, L.:** Proc. Central Soc. Clin. Research, **23,** 47, 1950.
36. **Horlick, L., Feldman, M., Jr.,** and **Katz, L. N.:** Proc. Soc. Exper. Biol. & Med., **68,** 243, 1948.
37. **Kempner, W.:** Bull. N. Y. Acad. Med., **22,** 358, 1946.
38. **Keys, A.:** In discussion of (46), at June, 1951 meeting of American Medical Association.
39. **Keys, A., Mickelsen, O., Miller, E. V. O.,** and **Chapman, C. B.:** Science, **112,** 79, 1950.
40. **Lyons, C.:** Am. J. Physiol., **98,** 156, 1931.
41. **Malmros, H.:** Acta med. scandinav., **246,** 137, 1950.
42. **Man, E. B.,** and **Gildea, E. F.:** J. Biol. Chem., **99,** 61, 1932.
43. **Mellinkoff, S. M., Machella, T. E.,** and **Reinhold, J. G.:** Am. J. Med. Sci., **220,** 203, 1950.
44. **Messinger, W. J., Porosowska, Y.,** and **Steele, J. M.:** Arch. Int. Med., **86,** 189, 1950.
45. **Morrison, L. M.:** J. Am. Med. Assn., **145,** 1232, 1951.
46. **Moses, C., Rhodes, G. L., Leatham, E.,** and **George, R. S.:** Circulation, (in press).
47. **Okey, R.,** and **Stewart, D.:** J. Biol. Chem., **99,** 717, 1933.
48. **Okey, R.,** and **Turner, E.:** Fed. Proc., **10,** 390, 1951.
49. **Oppenheim, E.,** and **Bruger, M.:** Am. J. Med. Sci., **205,** 77, 1943.
50. **Plotz, M.:** J. Am. Med. Assn., **139,** 623, 1949.
51. **Poindexter, C. A.,** and **Bruger, M.:** Arch. Int. Med., **56,** 884, 1935.
52. **Priddle, W. W.:** Ann. Int. Med., **35,** 836, 1951.
53. **Pucher, G. W.,** and **Sly, G. E.:** Bull. Buffalo Gen. Hosp., **1,** 10, 1929.
54. **Rabinowitch, I. M.:** Ann. Int. Med., **8,** 1436, 1935.
55. **Rinehart, J. F.,** and **Greenberg, L. D.:** Am. J. Path., **25,** 481, 1949.
56. **Rinehart, J. F., Moon, H. D.,** and **Greenberg, L. D.:** J. Geront., **6,** 141, 1951.
57. **Rosenthal, S. R.:** Arch. Path., **18,** 473, 660, 827, 1934.
58. **Russ, E. M., Eder, H. A.,** and **Barr, D. P.:** Am. J. Med., **11,** 468, 1951.
59. **Siperstein, M. D., Chaikoff, I. L.,** and **Chernick, S. S.:** Science, **113,** 747, 1951.
60. **Snapper, I.:** Nutrition and Nutritional Diseases in the Orient, in *Advances in Internal Medicine.* Lancaster, Interscience Press, Vol. 2, p. 596, 1947.
61. **Soper, H. W.:** Am. J. Digest. Dis. & Nutrition, **4,** 577, 1937.
62. **Starke, H.:** Am. J. Med., **9,** 494, 1950.
63. **Steiner, A.:** Am. J. Med., **6,** 103, 1949.
64. Idem: Geriatrics, **6,** 209, 1951.
65. **Steiner, A.,** and **Domanski, B.:** Am. J. Med. Sci., **201,** 820, 1941.
66. **Steiner, P. E.:** Arch. Path., **42,** 359, 1946.
67. **Unselm, E.:** Acta paediat., **11,** 533, 1930.
68. **Walker, W. J.,** and **Wier, J. A.:** Circulation, **3,** 864, 1951.
69. **Wilens, S. L.:** Arch. Int. Med., **79,** 129, 1947.
70. **Wilkinson, C. F., Jr., Blecha, E.,** and **Reimer, A.:** Arch. Int. Med., **85,** 389, 1950.

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MASSIVE BLEEDING FROM THE UPPER GASTROINTESTINAL TRACT

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WERE it not for the fact that during the past 10 years there has been a renewed surgical interest in the problem of bleeding from the upper gastrointestinal tract, this subject would be quite inappropriate for a discussion under the title of Progress in Surgery. The literature relating to upper gastrointestinal tract hemorrhage is voluminous[44,46,48,63], especially that which is concerned with bleeding from gastric and duodenal ulcer. The causes of bleeding from the upper gastrointestinal tract in order of frequency are: duodenal ulcer, gastric ulcer, esophageal varices, gastric carcinoma, gastritis, and a group of miscellaneous causes[10,13,14,30,70]. Bleeding from lesions within the stomach or duodenum and in which an accurate diagnosis has been made accounts for approximately 85 to 90% of all reported cases. Bleeding from esophageal varices accounts for approximately 5%. Significantly, this leaves but from 5 to 15% of the total number of cases in which the diagnosis is not well determined or arises from causes which are relatively infrequent[23,45,49]. Since bleeding from the upper gastrointestinal tract in the vast majority of cases results from peptic ulcer, it is not inconsistent that discussion of bleeding from the upper alimentary tract should be considered most extensively in relation to the ulcer problem.

In 1828 Abercrombie[2] stated that fatal hematemesis was rare, despite

the fact that he described 2 rather typical cases that died. The treatment described by Abercrombie is quite interesting in that it is similar to the treatment which is described in most textbooks of medicine or surgery. Aside from the drugs which Abercrombie used, most of which have not stood the test of time, there was little else prescribed except bed rest and diet. If such a patient were left to his own devices he would go to bed, especially when he felt weak and would eat when he was hungry. It is quite likely therefore that these cases would do just about as well if left to their own devices, than if carried under so-called treatment as that which was generally accepted some 10 years ago.

Certain fears based on theoretical rather than practical grounds have retarded the development of a rational approach to the problem of bleeding from the upper gastrointestinal tract. Despite the advocacy by several authors[6,31,47,68] that patients who were bleeding should be given food by mouth, the withholding of all oral intake was common until Meulengracht [53,54,55] popularized the feeding of these patients. Similar fears regarding the possibility of increasing hemorrhage prevented the general acceptance of the use of gastric intubation as a means of determining whether bleeding had stopped, or for treatment, despite its use by several authors[4,31,67]. It is amazing on what slim grounds many such fears arise. Even a fairly recent paper condemns the use of a Levine tube in the stomach because in a series of 300 cases[22] with a mortality of 25%, the tube was said to have produced fatal hemorrhage in 2 patients and to have increased it in several others. One patient died during lavage with ice water and the author condemns lavage as well as gastric intubation. The citing of inferential causes of death in a series of cases without evaluation of the seriousness of the hemorrhage is confusing, and sweeping conclusions drawn from such series add little to the problem.

Probably the most striking fear was related to the use of transfusions or administration of other fluids. As a rule, transfusions were strictly forbidden in cases of bleeding peptic ulcer except in cases where complete exsanguination was apparent. In some instances small transfusions were allowed. These were so small that they were not likely to be of any value for blood replacement.

Fairly reliable means for evaluating trends in treatment are to be found in average textbooks. The following excerpt from the 1931 edition of DaCosta[24] is fairly characteristic of the usual thought of that time. "Some claim that surgical treatment is not to be employed in gastric hemorrhage and that statistics are decidedly against it. I believe this statement to be correct. . . . Some care must be exercised in the restoration of blood volume. It is dangerous to increase blood pressure to a degree liable to dislodge clot. If symptoms of shock are alarming give transfusion small in quantity (150 to 200 cc.). A week or 10 days after the hemorrhage is past, 1 or more transfusions of 500 cc. are of the greatest value. . . . Shock is treated by absolute rest and morphine and blood replacement as above stated. . . . At end of 7 or 8 days regular ulcer diet is prescribed. Stimulation is avoided. Instrumentation or rough physical examination is avoided for 2 weeks." Reminiscent of the statement made by Abercrombie in 1828[2] is the following from the first edition of Christopher's Surgery, published in 1936[18]: "Absolute rest, with the foot of the bed elevated, external heat, reassurance of the patient and the use of sufficient

morphine to allay fear and secure quiet are indicated. No food or drinks should be given by mouth and starvation should be continued until so far as can be ascertained no bleeding has occurred for 48 hours. The mouth should be kept scrupulously clean. Water may be given by bowel and saline solution in moderate amounts administered by hypodermoclysis, to which may be added 2% glucose. Blood transfusion is contraindicated except as an adjunct to surgery, or in cases showing persistent and alarming exsanguination, as a life-saving measure. Rarely does the patient, especially the young patient with chronic ulcer, succumb to a first hemorrhage". In 1945, in the fourth edition[19], a similar discussion appeared as follows: "Bleeding may be coming from esophageal varices or from gastric lesions due to gastritis, ulcer, benign or malignant neoplasms. In any case the patient is put to bed, and attempts are made to keep him at complete rest. This means the judicious use of morphine to allay fear, reassurance of the patient and treatment for shock if necessary. The duodenum should be put at rest also by withholding food and fluid by mouth so that a clot may form and occlude the bleeding point. Fluids may be administered subcutaneously or by proctoclysis. Intravenous medication is to be avoided as it may raise the pressure sufficiently to dislodge a newly formed clot. Small transfusions of 50 to 75 cc. of blood may be used when anemia has reached an alarming level. This is more for the clotting effect than for the restoration of blood volume." In the fifth edition, 1950[20], the discussion of bleeding from duodenal ulcers is still the same with small transfusions of from 50 to 75 cc. of blood. However, in the discussion of gastric hemorrhage we find a new concept added. "In no situation is there greater need for the individualization of cases with respect to therapy than in that of gastric hemorrhage. If the hemorrhage is severe the life of the patient will depend upon the wisdom with which the physician evaluates the problem and utilizes the various therapeutic measures. *The treatment of shock, actual or impending, takes precedence over all other considerations.* . . . If the blood pressure is low, a transfusion of whole blood should be started as soon as possible and given rapidly until the pressure has returned to safe levels, usually a systolic pressure of 100 mm. of mercury or higher. Following a massive hemorrhage, as much as 1000 to 1500 cc. of blood may be given in the course of a few hours to stabilize the circulation. The danger of 'blowing off a clot' which may have formed on the bleeding vessel by raising the blood pressure suddenly from shock levels is of less consequence than the dangers of prolonged hypotension". In the sixteenth edition of the "Principles and Practice of Medicine" edited by Christian[17], 1947, the management of the patient bleeding with peptic ulcer is as follows: "When *hemorrhage* occurs no attempt should be made to check the hemorrhage by giving drugs by mouth; the essential point is to put the patient in bed at rest. If very restless, morphine in small doses may be given. The present author has found Sippy's method of treating hemorrhage very satisfactory. Sippy gave at once a powder of magnesium oxide, 4 gm., and calcium carbonate, 2 gm., and repeated this in ½ hour; then he gave calcium carbonate, 2 gm., every ½ hour for 8 to 10 hours. The next day he gave calcium carbonate every ½ hour and at night every hour. On the third day he began milk and cream feeding and gave powders as in nonbleeding cases; subsequently his reg-

ular regimen was followed . . . Not infrequently the loss of blood is so great that the patient faints, but a fatal result is not very common. Transfusion of blood is advisable in severe conditions, but in the majority of patients it can be dispensed with; it may start up a subsiding bleeding. General signs of collapse are more important than blood counts in determining transfusion. Very often frequent blood pressure determinations and other examinations unduly exhaust the patient, while giving no valuable information in determining what should be done. Few surgeons now operate as a means of treating the bleeding ulcer patient. The patients usually recover rapidly from the hemorrhage; many later require iron in full doses. The present author's policy has been to treat the bleeding ulcer without blood transfusions except in a rare instance of continuing or of very massive bleeding. The results from this policy have seemed quite as good as those obtained with the frequent use of transfusion, and it saves the work and expense incident to blood transfusions and does away with the danger of post-transfusional reactions. Others transfuse early and frequently". The seventh edition of Cecil's Textbook, 1947[15], presents a somewhat different concept from the other texts quoted in that transfusion is recommended. "The time-honored therapy in massive hemorrhage is bed rest, elevation of the foot of the bed, application of an ice-bag to the epigastrium, morphine in doses adequate to quiet the restlessness, and complete starvation for several days. Immediate feeding has been found to be superior to starvation. Blood transfusions allay the restlessness and hence morphine is rarely necessary. The blood pressure and the pulse rate should be watched carefully, reading being taken at hourly or half-hourly intervals. The blood count does not usually drop until several hours after the initial hemorrhage and hence is not as good an index of the severity of the bleeding as are the blood pressure and the pulse rate."

"*Blood transfusion* is indicated when the pulse rate exceeds 120 per minute and the blood pressure drops below 90 or even 100 mm. of mercury. When the bleeding takes place slowly and continuously, the pulse rate and blood pressure may not reach these levels and yet transfusion may be indicated because of the anemia. If the erythrocyte count is below 3,000,000 cells per cubic millimeter, transfusion is desirable; if it is below 2,000,000 cells, transfusion is imperative. Many patients recover spontaneously from such levels, but their margin of safety is very narrow and a relatively small hemorrhage may prove fatal. The blood should be matched most meticulously. Each transfusion should consist of 500 or 600 cc. of whole blood and as many should be given as necessary. The greater the number of transfusions required, the graver the prognosis, not because the transfusions are harmful, but because the great need for them constitutes evidence that a large and probably sclerotic vessel is the source of the bleeding."

It is apparent from these excerpts, except the last mentioned, that the treatment described for a bleeding ulcer is the treatment of a complication of the ulcer, whereas actually the problem is one of blood loss. The treatment of the ulcer in these cases is of very secondary importance. Treatment usually has not been designed on the basis of sound principles for control of hemorrhage. Until recent years little thought was given to adequate blood replacement or sound principles of hemorrhage control. As far back as 1901, Mayo-Robson[51] pointed out that

aside from the matter of accessibility and diagnosis, the treatment of the bleeding ulcer ought to be the same as the bleeding from a radial or tibial artery. A similar view has more recently been expressed by Holman[41]. What, then, are some of the reasons for a difference in concept in the handling of the patient bleeding from a duodenal ulcer as compared with that from a more exposed part? The first, of course, is the difficulty of determining the source and severity; the second is the difficulties encountered in controlling the hemorrhage. In relation to determination of the source of the hemorrhage it might be said that on a purely statistical basis, one can be sure in at least 85% of the patients the bleeding arises in an ulcer of the stomach or duodenum. Furthermore, on a purely statistical basis, one can be relatively sure that in the majority of the cases the bleeding will be from a *posteriorly placed* duodenal ulcer[43,48]. While this is quite logical reasoning, it does not indicate in an individual case the exact source of the bleeding.

Cases bleeding from esophageal varices, which are a very troublesome group with a high mortality[39], can be determined by the double lumen tube first described by Patton and Johnston[26,59] and later by Sengstaken and Blakemore[66]. With the Patton tube in place and the balloons inflated, if the bleeding is from esophageal varices, it is not only possible to stop the bleeding but one can also differentiate between esophageal bleeding and bleeding from the stomach or duodenum. With the tube inflated the stomach may be washed clear of blood or blood clots. If bleeding continues after tamponade on the lower end of the esophagus, the source of the bleeding must be the stomach or the duodenum. Cases of bleeding from the small bowel below the duodenum are rare, especially those in which blood is found in the stomach. This is exceedingly important, since the mortality rate from acute blood loss in esophageal varices is high, while that from the stomach or duodenum is usually low unless massive hemorrhage is encountered.

When necessary in making a differential diagnosis, barium studies may be made[32,37,64,77] and there need be no fear of causing added difficulties by this procedure. In our hands, however, the use of barium studies has been rarely necessary or advantageous.

The determination of the severity of the bleeding imposes several problems. It has frequently been pointed out that the hemoglobin levels are of no value in determining the amount of blood lost, nor is the total red cell count or the hematocrit[62,69,72]. In severe acute blood loss sufficient time has usually not elapsed to permit hemodilution and one is much more likely to be determining chronic blood loss by the time such changes take place. In ordinary clinical practice, a determination of circulating blood volume is usually not done on a routine basis. If it were, this would be of value. It has been constantly pointed out that any estimation of the amount of blood loss by attempting to evaluate the amount vomited or lost in the stool is at best a very rough guess[27,65]. The usual concept is that the amount of blood estimated by this means is usually greater rather than less than actual, because of the dilution with gastrointestinal fluids. It should be remembered that it is rather unusual for the patient to vomit or to pass at any one time all of the blood lost, so that one estimates only a portion of the hemorrhage.

The usual methods for determining the severity of blood loss, therefore, are poor at best, and one is left with

the generalization that one must depend upon the reaction of the patient to determine the amount lost. The blood pressure in itself as a single determination is not definitive, but if persistently low, is highly suggestive. Coupled with marked pallor, deep sighing respiration, and a soft, fast pulse, it forms a fairly good indication that the amount of blood loss has been acute and severe. If this is associated with loss of consciousness which persists for any length of time, it is a good indication that the blood loss has been quite marked. While this means of evaluation of the patient so far as blood loss is concerned is fairly effective in determining the need for prompt blood replacement, it does not form a reliable method of classification, and classifications based upon the reactivity of the patient will vary from one observer to another. Using any such classification of this sort it is quite impossible to compare the results of one group of observers with that of another. In addition to a determination of the severity of bleeding, it is important to be able to determine in which patient the bleeding has stopped, and once this is known, to be able to know definitely when bleeding recurs. A patient may lose a moderate amount of blood from a vessel exposed in an ulcer, may stop bleeding entirely, and then within a short time may bleed again. It is this sort of case which gives concern, because repeated fair-sized hemorrhages over a period of several days usually cause not only a greater difficulty in the evaluation in the amount of blood lost, but more important, they are likely to cause a greater drain on the patient's blood stores than is a single massive hemorrhage. It is this type of patient who has stopped short of exsanguination over a period of several days which results in the greatest mortality[3,5,8,9,11,16,29,33,35,36,38,40,41,42,56,57,61,75,76] and which have in the past caused many to consider that operative intervention was hopeless[1,24,52]. Even though it is possible to replenish the circulating blood volume in patients who have bled excessively over a period of several days, it is not possible promptly to replenish by transfusion the marked loss from the tissue stores[60]. Accordingly in late cases, even if sufficient blood replacement can be supplied to keep the circulation intact during the operative procedure, the period following operation is quite likely to be stormy on the basis of anoxia in the tissues. [See P.S.]

The difficulty of the approach to the source of bleeding in the majority of these cases has been one great deterrent to operative intervention. Quite obviously one must select only those cases in which there is necessity of controlling the hemorrhage. The majority of cases bleeding from a duodenal or gastric ulcer will be found to have lost minimal or moderate amounts of blood. One might compare these to the blood loss from small lacerations. On the exposed parts where there are only small capillaries, venules or arterioles cut, or possibly bleeding from a small vein, this might be controlled by doing nothing at all and frequently requires not even compression to stop the hemorrhage. Small to moderate sized arteries on the exposed surfaces frequently will stop bleeding before the patient has lost more blood than he can easily withstand. When a large artery, however, is cut it is rather unusual for retraction of the vessel with clotting to occur sufficiently early that the patient's life is not in danger. One would therefore not consider minimal amounts of bleeding from a superficial wound as requiring very energetic surgical measures any more than would minimal or moderate amounts of bleeding from the gastrointestinal tract.

Much has been said in relation to the age relationship regarding the question of operative control of hemorrhage from ulcers. Young patients, as well as old patients, will bleed to death if the hemorrhage is great enough and the age of the patient cannot be a criterion for or against operation. The concept that the younger patients' blood vessels will retract and constrict sufficiently to stop the hemorrhage does not appear to be a reasonable thesis to those who have seen the usual amount of scar about such vessels[28], and the reason for the lower mortality in young individuals as compared to older is more likely that they stand blood loss better.

In order to approach the bleeding point in cases bleeding from the stomach or duodenum, an abdominal operation is necessary and the easiest approach to the bleeding area is usually a gastrectomy. Actually the operative procedure necessary to find and ligate the bleeding vessel is usually more of a problem than is gastrectomy. The bleeding points are often not easily found, and if found are usually imbedded in scar so that the ligation of the vessel is fraught with difficulty. Most surgeons therefore agree that a gastrectomy is the simplest approach[12,21,34,40,50,58,69,71,73,74] and makes control of the hemorrhage and location of the vessel easier. The fact that the patient is likely to be relieved of his ulcer following such a procedure can only be of secondary importance, since the primary reason for the operation is the control of the hemorrhage. Much of the reticence about operating upon these patients has been coupled with mortality from gastrectomy. Mortality from gastrectomy has gradually decreased, so that today, while still a formidable procedure, is not nearly so severe an ordeal as it was even so short a time as 15 or 20 years ago. Furthermore, this procedure has become fairly standard, so that it is commonly performed in almost all hospitals, whereas formerly it was reserved for larger centers. The fear of performing a gastrectomy in the face of an early massive hemorrhage is less today than formerly, because of the widespread use of blood transfusions for immediate replacement of blood loss. The mortality from gastrectomy in good hands in a patient suffering from marked acute blood loss should be no different than the mortality from a gastrectomy in the same patient providing it is possible to replace volume for volume and promptly the amount of blood which has been lost. That our concepts with regard to the care of patients who are bleeding massively from the upper gastrointestinal tract have changed within the past few years is obvious. No longer can we be satisfied with the treatment of bleeding from the upper gastrointestinal tract as just another problem in the management of the ulcer patient. Our concepts must be directed to the control of hemorrhage without concern for the ulcer. Once a hemorrhage has been controlled, the patient is then a problem of ulcer management and this management must be designed to prevent recurrence of the ulcer, which may perchance bleed if it recurs. If these two concepts are not considered separately, the result can only be a continued high mortality from bleeding from the upper gastrointestinal tract when bleeding is severe.

Data are of no importance for evaluation if when added to the cases of severe bleeding one includes a large number of patients suffering from minimal amounts of hemorrhage and arrives at a low mortality. Significant are the data which have been presented by Brown *et al.*[13]. They studied 246 cases of bleeding from the upper gas-

trointestinal tract as a result of peptic ulcer. They divided their cases into 4 different groups, based chiefly on the severity of bleeding. In all their patients in Groups 1 and 2 which comprise patients with minimal or moderate amounts of blood loss as evidenced by the reaction of the patient, the mortality was low, even though as a rule these patients were not transfused. In the severely bleeding patients, classed as Group 4, there was a mortality of 86% when treated without surgical intervention. There were 11 cases referred to surgery as a last resort for an emergency operation. In this group, despite the fact that they represented the worst possible candidates for surgery in that they had been exsanguinating for several days, the mortality was 18%. The significant comparison between surgical and non-surgical treatment is to be had by comparing the same type of case. It is to be pointed out that the cases listed in the report of Brown *et al.* which were treated surgically were considered to be medical failures, and it must also be assumed that the 87% which died without surgical intervention were not operated upon because they died before they were seen by a surgeon or were not considered viable enough when seen to offer any chance of withstanding the surgical measures necessary to control the hemorrhage. Accordingly, the 18%, which represents a high mortality for surgical intervention except when considered in the light of a last ditch stand, might be considered as those not possible to salvage by any means after their long period of exsanguination.

In a study of any reported series where surgical intervention is compared with non-surgical treatment, it is important to determine whether the results from surgery are from those cases which are failures after prolonged medical management or those which are selected for surgical treatment early. A much brighter picture has been presented recently by Stewart[69]. Stewart's philosophy in relation to bleeding from the upper gastrointestinal tract is a very simple and plausible one and is similar to that expressed by Finsterer[33]. Stewart observes that patients with marked acute blood loss will stand operative procedures well if the blood loss is replaced promptly. This observation is one which became so apparent during World War II in that prompt and effective replacement of blood permitted major surgical procedures to be carried out successfully[7], whereas delay in replacement or long continued blood loss does not permit of such happy outcome. Stewart[69] believes that patients who have lost as much as one-third of their circulating cell mass from bleeding from the upper gastrointestinal tract should be operated upon promptly to control the loss of blood and his reported mortality is 10.7% of 65 patients, while among 42 who refused operation the mortality was 21.4%.

At the Detroit Receiving Hospital all cases of bleeding from the gastrointestinal tract are admitted to the surgical wards on the basis that control of hemorrhage is of primary importance. If there is any question as to the source of bleeding from the upper gastrointestinal tract, a Patton tube is inserted, the lower esophagus tamponaded, and the stomach washed with buffer-thrombin[25]. If the washings continue to return bloody, after preliminary washing, additional thrombin buffer is added. If the patient shows clinical signs of exsanguination not promptly headed toward correction by transfusion, immediate operation is considered. If the bleeding has obviously stopped as evidenced by the gastric washings, buffer is continued and transfusions are given to correct the blood loss. While buffer-thrombin appears to control hemorrhage in some

instances, it is considered an important adjunct, primarily because it permits us to determine whether or not bleeding has stopped. The buffer also decreases the possibility of clot digestion. If the bleeding recurs after having stopped and while under adequate treatment, emergency operation is considered, regardless of the interval between the episodes. We feel, as do most surgeons that operations upon patients who have been subjected to a drain on their blood stores for a prolonged period present a serious problem. Patients who stop bleeding and whose hemoglobin and blood volume have been restored to near normal levels are considered as ulcer patients and are evaluated for therapy without regard to the bleeding episode.

The question of the need for operative intervention and the timing of the procedure is one in which there is wide variation of opinion. Opinions vary from immediate surgical intervention for patients bleeding severely to the use of surgery only after other measures have failed. Some authors adhere to the 48-hour rule of Finsterer[33], while others do not consider the time element of much importance. Fixed routines for management are much less in evidence than formerly, and individualization of the patient's problem is often recommended. The amount and rate of blood loss, the reaction of the patient and the facilities at hand for treatment are considerations which are important.

The change in the philosophy of the management of cases bleeding massively from peptic ulcer relates chiefly to the acceptance of the concept that a more vigorous approach to the problem is possible. The fear of food intake when these patients can and will eat has been fairly well dissipated. There is no longer a general fear that gastric intubation, intravenous infusions, or Roentgen ray studies with a barium meal will precipitate, reactivate or increase bleeding in these patients. The concept that these patients represent primarily problems in hemorrhage rather than problems in ulcer management dictates that vigorous steps be taken to stop the hemorrhage and to replace the blood loss. This represents a fundamental surgical concept and is one which many internists have also accepted in relation to the management of these cases.

P.S. A paper published after this review went to press (H. H. LeVeen, H. G. Mulder and F. Prokop: Surg., Gynec., & Obst., **94**, 433, 1952) indicates that in massive bleeding from the gastroduodenal artery the blood pressure in the hepatic artery falls far below that in the peripheral arteries. This suggests that anoxia of the liver is likely to be associated with massive hemorrhage from duodenal ulcer.

REFERENCES

(1) **Aaron, C. D.**: Diseases of the Digestive Organs, 4th ed., Philadelphia, Lea and Febiger, 1927, p. 497. (2) **Abercrombie, J.**: Diseases of the Stomach, the Intestinal Canal, the Liver and Other Viscera of the Abdomen, Edinburgh, Waugh and Ives, 1828, p. 80. (3) **Allen, A. W.**, and **Benedict, E. B.**: Ann. Surg., **98**, 736, 1933. (4) **Amendola, F. H.**: Ibid., **129**, 47, 1949. (5) Idem: Surg., **31**, 340, 1952. (6) **Andresen, A. F. R.**: J. Am. Med. Assn., **89**, 1397, 1927.

(7) **Beecher, H. K.**: Ann. Surg., **121**, 769, 1945. (8) **Best, R. R.**: Nebraska State Med. J., **35**, 11, 1950. (9) **Blackford, J. M.**, and **Williams, R. H.**: J. Am. Med. Assn., **115**, 1774, 1940. (10) **Bockus, H. L.**: Gastroenterology, Philadelphia, W. B. Saunders Co., 1944, p. 559. (11) **Bohmansson, G.**: Acta chir. scand., **94**, 362, 1946. (12) **Bohrer, J. V.**: Ann. Surg., **114**, 510, 1941. (13) **Brown, J. R., Meyers, S. G., Posch, J. L.**, and **Deneen, O.**: Arch. Surg., **61**, 767, 1950. (14) **Bulmer, E.**: Lancet, **2**, 720, 1932.

(15) **Cecil, R. L.**: A textbook of Medicine, 7th ed., Philadelphia, W. B. Saunders Co., 1947, p. 797. (16) **Chinn, A. B.**, and **Weckessar, E. C.**: Ann. Int. Med., **34**, 339, 1951. (17) **Christian, H. A.**: The Principles and Practice of Medicine, 16th ed., New York, Appleton Century Co., 1947, p. 665. (18) **Christopher, F.**: A Textbook of Sur-

gery by American Authors, 1st ed., Philadelphia, W. B. Saunders Co., 1936, p. 1167. (19) **Christopher, F.**: A Textbook of Surgery by American Authors, 4th ed., Philadelphia, W. B. Saunders Co., 1945, p. 1002. (20) **Christopher, F.**: A Textbook of Surgery by American Authors, 5th ed., Philadelphia, W. B. Saunders Co., 1950, p. 960. (21) **Cole, W. H.**: Surg. Cl. N. America, **31**, 271, 1951. (22) **Costello, C.**: Ann. Surg., **129**, 289, 1949. (23) **Crohn, B. B., Marschak, R. H.**, and **Galinsky, D.**: Gastroenterology, **10**, 120, 1948.

(24) **DaCosta, J. W.**: Modern Surgery, 10th ed., Philadelphia, W. B. Saunders Co., 1931, p. 887. (25) **Daly, B. M.**: Arch. Surg., **55**, 208, 1947. (26) **Daly, B. M., Johnston, C. G.**, and **Penberthy, G. C.**: Ann. Surg., **129**, 832, 1949. (27) **Daniel, W. A., Jr.**, and **Egan, S.**: J. Am. Med. Assn., **113**, 2232, 1935. (28) **Deaver, J. B.**, and **Ashhurst, A. P.**: Surgery of the Upper Abdomen, 2nd ed., Philadelphia, P. Blakiston's Son and Co., 1921, p. 82. (29) **Dunphy, J. E.**, and **Hoerr, S. O.**: Surg., **24**, 231, 1948.

(30) **Eads, J. T.**: J. Am. Med. Assn., **131**, 891, 1946. (31) **Einhorn, M.**: Med. J. and Rec., **135**, 219, 1932. (32) **Elmer, R. A., Rousuck, A. A.**, and **Ryan, J. M.**: Gastroenterology, **16**, 552, 1950.

(33) **Finsterer, H.**: Surg., Gynec. & Obst., **69**, 291, 1939.

(34) **Glenn, F.**, and **Harrison, C. S.**: Arch. Surg., **63**, 766, 1951. (35) **Gordon-Taylor, G.**: Lancet, **2**, 811, 1935. (36) **Gordon-Taylor, G.**: Brit. J. Surg., **25**, 403, 1937-38.

(37) **Hampton, A. O.**: Am. J. Roent., **38**, 565, 1937. (38) **Heuer, G. J.**: New Eng., J. Med., **235**, 777, 1946. (39) **Higgins, W. H.**: Am. J. Med. Sci., **214**, 436, 1947. (40) **Holloway, J. B., Jr., Armour, T., Jr.**, and **Proctor, W. H., Jr.**: Arch. Surg., **61**, 487, 1950. (41) **Holman, C. W.**: Surg., **23**, 405, 1948. (42) Idem: Surg. Clin. N. Am., **30**, 421, 1950. (43) **Hurst, A. F.**, and **Stewart, M. J.**: Gastric and Duodenal Ulcer, 1st ed., London, Oxford University Press, 1929, p. 252.

(44) **Ivy, A. C., Grossman, M. I.**, and **Bachrach, W. H.**: Peptic Ulcer, 1st ed., Philadelphia, The Blakiston Co., 1950, p. 934.

(45) **Jankelson, I. R.**, and **Milner, L. R.**: J. Am. Med. Assn., **145**, 17, 1951. (46) **Jones, F. A.**: Gastro-enterology, 1st ed., New York, Paul B. Hoeber, 1952, p. 432.

(47) **Lenhartz, H.**: Deutsche med. Wchnschr., **30**, 412, 1904. (48) **Lewison, E. F.**: Int. Abst. Surg., Coll. Rev., **90**, 1, 1950. (49) **Loe, R. H.**: Arch. Surg., **61**, 183, 1950.

(50) **MacKinnon, D. C.**: Minnesota Med., **33**, 244, 1950. (51) **Mayo-Robson, A. W.**, and **Moynihan, B. G. A.**: Diseases of the Stomach and their Surgical Treatment, New York, William Wood and Co., 1901, p. 137. (52) **McLean, H.**: Modern Views on Digestion and Gastric Disease, 2nd ed., London, Constable and Co. Ltd., 1928, p. 176. (53) **Meulengracht, E.**: Acta med. scandinav. (Suppl.) **59**, 375, 1934. (54) Idem: Brit. Med. J., **2**, 321, 1935. (55) Idem: Arch. Int. Med., **80**, 697, 1947. (56) **Miller, T. G.**, and **Elsom, K. A.**: Med. Cl. North Am., **22**, 1711, 1938.

(57) **Needham, C. D.**, and **McConachie, J. A.**: Brit. Med. J., **2**, 133, 1950.

(58) **Parsons, K. O.**, and **Aldridge, L. W.**: Brit. J. Surg., **38**, 370, 1951. (59) **Patton, T. B.**, and **Johnston, C. G**: Arch. Surg., **59**, 502, 1949. (60) **Porter, M., Harvey, H. D.**, and **Schullinger, R. N.**: Arch. Surg., **60**, 1076, 1950.

(61) **Rose, F.**: Deutsche med. Wchnschr., **76**, 41, 1951. (62) **Rudman, I.**, and **Stewart, J. D.**: Surg., **28**, 170, 1950.

(63) **Sandweiss, D. J.**: Peptic Ulcer, 1st ed., Philadelphia, W. B. Saunders Co., 1951, p. 623. (64) **Schatzki, R.**: New Eng. J. Med., **235**, 783, 1946. (65) **Schiff, L., Stevens, R. J., Shapiro, N.**, and **Goodman, S.**: Am. J. Med. Sci., **203**, 409, 1942. (66) **Sengstaken, R. W.**, and **Blakemore, A. H.**: Ann. Surg., **131**, 781, 1950. (67) **Soper, H. W.**: J. Am. Med. Assn., **97**, 771, 1931. (68) **Spriggs, E. I.**: Brit. Med. J., **1**, 825, 1909. (69) **Stewart, J. D., Rudman, I., Citret, C.**, and **Hale, H. W.**: Ann. Surg., **132**, 681, 1950. (70) **Sullens, W. E., Steigmann, F.**, and **Meyer, K. A.**: Arch. Surg., **59**, 1244, 1949.

(71) **Tanner, N. C.**: Royal Soc. Med. Proc., **43**, 147, 1950.

(72) **Walsh, R. J.**, and **Sewell, A. K.**: Med. J. Australia, **1**, 73, 1946. (73) **Walters, W.**, and **Cleveland, W. H.**: Ann. Surg., **114**, 481, 1941. (74) **Wangensteen, O. H.**: **Surg., 8**, 275, 1940. (75) **Warren, R.**, and **Lanman, T. H.**: Surg., Gynec. & Obst., **87**, 291, 1948. (76) **Welch, C. E.**: J. Am. Med. Assn., **141**, 1113, 1949.

(77) **Zamcheck, N. Chalmers, T. C., Ritvo, M.**, and **Osborne, M. P.**: J. Am. Med. Assn., **148**, 504, 1952.

OPHTHALMOLOGY

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AMAUROSIS FUGAX

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MOMENTARY obscurations of vision, such as those which occur intermittently in the presence of increased intracranial pressure and, usually, chronic choked disks, result probably from temporarily inadequate blood supply to the retinas. The loss of vision which precedes fainting, that which is noted in some patients with postural hypotension after prolonged standing, in cases of massive bleeding from the gastrointestinal tract or elsewhere, and in the "blackouts" of aviators, all seem to be on the same basis. Lowering of cerebral or general blood pressure is responsible for the loss of vision. Under experimental conditions, it has been demonstrated, as noted by Behrman[3], that loss of vision without loss of consciousness occurs when the systolic blood pressure at head level falls to just under 20 mm. of mercury. It seems logical to assume that "blackout" will occur whenever the cerebral blood pressure falls below the intra-ocular pressure. In cases of "blackout" of these types, vision is recovered rapidly as a rule without residual field defects. In some instances, however, particularly in patients who have had repeated massive hemorrhages or who have severe retinal arteriolosclerosis, the inadequacy of the retinal blood supply may be sufficiently prolonged to result in permanent partial or total blindness without ophthalmoscopic evidence of closure of a retinal arteriole or of the central artery of the retina.

Although the loss of vision in the previously described types of cases is ordinarily transient or fleeting, it is not generally spoken of as "amaurosis fugax." This term is used by most authors now to identify a more limited group of cases in which the reduction of blood supply to the retina results primarily from a local disturbance in the retinal arteries or arterioles and not from a lowering of cerebral or general blood pressure. Thus, though Duke-Elder[7] defines amaurosis fugax simply as "temporary obscurations of vision," this designation appears in the section on retinal angiospasm. In Walsh's[20] text also, the term is used in the description of attacks of retinal angiospasm. Again, when Fisher[10] stated, "Intermittent monocular blindness due to retinal anemia constitutes a large fraction of what has been labelled amaurosis fugax, and it is probably better known under that name," he seemed to be referring to transient attacks of blindness due to local retinal or at least cerebral vasoconstriction. This review is particularly concerned

with cases in which a diagnosis of amaurosis fugax can be made in this restricted sense.

Characteristic Symptoms. Patients with the characteristic syndrome of amaurosis fugax complain of periodic, recurrent episodes of loss of vision in one eye. The loss of vision may be total or it may involve only a portion of the visual field. In the latter event, the same portion of the field is involved in each attack. In most instances the episodes occur in one eye only. Occasionally, episodes occur in each eye, but at different times. The attacks occur with varying frequency, sometimes as often as several times a day, sometimes only at intervals of a month or more. Between attacks the vision is normal and there are no diagnostic lesions in the ocular fundi. The duration of the visual loss also varies from a few seconds to several minutes. It is doubtful if episodes of total or partial blindness lasting longer than ten minutes can be classified as true amaurosis fugax, though in a few cases, such as that of Rosenstein[17], the blindness is said to have lasted as long as 45 minutes with complete recovery of vision. However, the retinal arterioles did not appear ophthalmoscopically to be entirely empty in this case. In some instances after a time, the episodes cease to occur. In perhaps the majority of cases, however, after a number of attacks, the vision fails to return within the usual time limit and closure of the central artery of the retina or of a branch arteriole is seen ophthalmoscopically. Under such circumstances, the loss of vision is usually permanent.

The length of time for which complete arrest of the circulation to the retina can persist without permanent loss of vision has not been definitely established. The ganglion cells of the retina will probably degenerate if their blood supply is completely cut off for as long as 6 or 7 minutes; but it is not possible to state definitely on the basis of ophthalmoscopic examination if the blood flow in the retina is entirely abolished. In fact, in most cases of arteriolar or arterial occlusion, it is probable that there is at least a minimal flow of blood except perhaps at the exact moment of the occlusion. At the time most of such cases are first seen, this minimal circulation is evidenced by the streaming of blood corpuscles in the arterioles or veins or both. Davenport[5] stated that according to de Schweinitz, a "cherry red spot" can develop in the macula within 10 minutes after the arrest of retinal circulation. Though the "cherry red spot" and the ischemic appearance of the retina supplied by the occluded vessel are commonly considered to be evidence of degeneration of the ganglion cells surrounding the fovea, they can be produced at times probably by simple edema of the retina. Otherwise it would not be possible for recovery of vision to take place as it did in Coston's[4] patient following block of the stellate ganglion approximately 5½ hours after an embolic occlusion of the superior temporal arteriole.

Associated Disease Processes. Some individuals with amaurosis fugax have elevated blood pressure or demonstrable vascular disease in the retina and in other parts of the body; some have cardiac murmurs. Still others, however, are young persons who present no evidence of either local retinal or generalized vascular disease. Migraine has been considered as the possible etiologic factor in at least some of the members of this last group.

The site of involvement in cases of so-called uremic or eclamptic amaurosis (which are sometimes included under the title of amaurosis fugax) is probably the occipital cortex. A period of total blindness is followed by a pe-

riod of right or left homonymous hemianopsia and then by complete recovery of vision. Likewise in migraine, the occipital cortex is presumed to be the site of origin of the scintillating scotomas and transient disturbances of vision which are usually homonymous in type. Engel, Ferris and Romano[8] demonstrated, in patients with migraine, that electro-encephalographic abnormalities were present in one occipital lobe during episodes of scintillating scotomas and homonymous field defects and that they were no longer present when the scotomas disappeared. It is known that in rare cases of apparently uncomplicated migraine permanent hemianopsia may follow a number of transient attacks presumably as the result of post-angiospastic cerebral infarction. In most cases of migraine, both eyes are involved simultaneously. However, some authors, among them Graveson[11], Grönvall[12] and Walsh[20] think that transient monocular scotomas or amaurosis can be of migrainous origin and that they can at times leave permanent residuals with ophthalmoscopic evidences of arterial or arteriolar occlusion. As a result of such observations, Behrman[3] states: "Personally, I feel that in most cases of migraine in which obscuration of vision alone is the chief manifestation the visual disorder is the result of vasoconstriction of retinal arteries, rather than of cerebral arteries." The weight of evidence would seem to indicate, however, that retinal vascular spasm is the exception rather than the rule in typical migraine.

The presence of chronic endocarditis in some patients with amaurosis fugax led to the supposition that small emboli lodging temporarily in the central artery or one of the arterioles of the retina might account for the periodic attacks of loss of vision. In most such cases, however, it was not possible to demonstrate any activity in the cardiac valvular lesion or any probable source of emboli. In 1927, Gipner and I[19] reported 5 cases which we concluded represented spasms of branch retinal arterioles in spite of the fact that in 3 of the 5 cases inactive cardiac valvular lesions were present. In 1 of these 3, the active spastic closure of the arteriole was observed ophthalmoscopically, but permanent occlusion did not occur at least during the period of observation. Three of the 5 patients gave a history typical of amaurosis fugax; only 1 of these 3 had chronic endocarditis. Of a group of 11 other cases of amaurosis fugax recorded in the files of the Mayo Clinic, in only 1 did the patient have a cardiac valvular lesion. This low incidence of endocarditis (14 per cent) would suggest that angiospasm is a more logical explanation than repeated emboli for the transient episodes of loss of vision. Further supportive evidence for the role played by angiospasm in these cases is furnished by the clinical experience that vasodilator drugs will shorten some of these attacks.

Mechanism of Retinal Angiospasm. Most observers agree now that recurrent arterial or arteriolar spasms account for the majority, if not all, of the typical cases of amaurosis fugax. By what mechanism the spasms are induced has never been adequately explained, however. That few if any of these cases represent instances of Raynaud's disease involving the retina is suggested by the fact that complaints of transient blurring of vision are very rare in cases of typical Raynaud's disease and that symptoms suggestive of Raynaud's disease are rarely complained of by patients with amaurosis fugax. Thus, of the previously mentioned 14 patients with permanent vascular occlusions following attacks of amaurosis fugax, only 2 had Ray-

naud-like symptoms in the extremities.

The vascular spasms in cases of amaurosis fugax seem to be of the type which Pal[16] designated maximal or occlusive. He suggested that such spasms resulted from excitation of vasoconstrictor nerves, from direct stimulation of contractile fibers, or from irritation of the intima by small emboli. The existence of a vasoconstrictor nerve supply to the retinal vessels or of contractile fibers in their walls has never been conclusively demonstrated. In 1939, I[18] reported 2 cases which seemed to show that, in the presence of a plaque of arteriosclerosis or atherosclerosis in the central artery of the retina or in one of its branches, irritative spasm might be induced in the arterioles distal to the plaque. A third case, which I observed in 1947, seemed to demonstrate this mechanism more conclusively than the first 2.

Case Report. A man, aged 45 years, had had 3 definite episodes of "transient blindness" in the right eye. Recovery had been complete after the first episode but incomplete after the second with no further permanent loss after the third. Vision of the right eye was reduced to ability to count fingers, and examination of the visual fields revealed nasal anopsia with central scotoma. Vision of the left eye was 6/6 and ability to read 14/14. The left fundus was normal. The right optic disk was pale (grade 2 to 3) and the retinal arterioles were generally narrowed (grade 2). A plaque of sclerosis was visible in the primary inferior branch of the central retinal artery. During the course of the ophthalmoscopic examination, the inferior macular branch arteriole could be seen to alternately empty and refill with blood within a few seconds. That the emptying of the arteriole was due to spastic constriction at its point of origin from the main inferior artery and not to temporary lowering of blood pressure beyond the arteriosclerotic plaque was suggested by the fact that the other branches of the inferior artery remained well filled with blood during the entire period of examinations by several observers.

It is possible that spasm of the retinal arterioles, distal to the region of organic arterial disease, may be a factor in the rapid onset of blindness in some cases of temporal or cranial arteritis. But it is doubtful that typical amaurosis fugax occurs in this disease. The basic factor which accounts for the loss of vision in these cases is narrowing of the lumen of the ophthalmic or central retinal artery by the inflammatory (or degenerative) process, with ultimate thrombotic occlusion of the severely constricted lumen. In most instances, after the onset of blindness, the ophthalmoscopic picture is that of ischemic optic neuritis and not of arterial or arteriolar occlusion. This results probably from gradual diminution of the blood supply to the optic nerve rather than from sudden vasospasm. There is no clinical evidence that vasodilator drugs prevent or reduce the degree of ultimate loss of vision in these cases.

Syndrome of Carotid Artery Occlusion. Recently, Fisher[10] has reported 7 cases in which recurrent transient monocular blindness was associated with contralateral hemiplegia. In 6 of these he attributed the condition to spontaneous thrombosis of the cervical portion of the internal carotid artery. He stated that the attacks of blindness usually preceded the stroke "as a sort of warning that disaster threatened." He thought, as a result of his observations, that "Disease of the internal carotid artery will no doubt help to explain at least some of the previously reported cases of amaurosis fugax, particularly in the older age groups." It is of interest that in discussing the mechanism of amaurosis fugax Behrman[3] had stated, apparently without definite proof, "Carotid arteriograms have revealed unsuspected occlusion of the internal carotid artery. I would postulate an occluding pathological

process affecting the internal carotid or ophthalmic artery as the explanation in some of these cases of amaurosis fugax."

The syndrome characteristic of spontaneous thrombosis of the internal carotid artery has usually been considered to consist of blindness in the homolateral eye, with the early ophthalmoscopic picture of closure of the central retinal artery and later optic atrophy, contralateral hemiplegia and hemianesthesia, aphasia in left-sided lesions, and, at times, temporal anopsia in the contralateral eye. According to Walsh[20], ligation of the internal carotid artery causes contralateral hemiplegia in only about 25% of cases. Blindness in the homolateral eye occurs much less frequently, probably because of the extensive and effective anastomotic connections between the ophthalmic artery and the branches of the external carotid artery on the same and on the opposite side. However, according to King and Langworthy[13], "When spontaneous closure of the carotid arteries on one side occurs, the thrombus may extend from the origin of the common carotid through the internal carotid, the ophthalmic and part of the middle cerebral artery. This seriously limits the pathways for collateral circulation and produces a more constant anatomic lesion in the brain." They expressed the thought that loss of vision in the homolateral eye results from closure of the ophthalmic artery with subsequent optic atrophy.

Although Fisher was the first to stress the occurrence of episodes of transient loss of vision in one eye (which might alternate with transient attacks of aphasia or of contralateral paralysis and paresthesia) in association with spontaneous thrombosis of the internal carotid artery[9], this symptom had been mentioned occasionally before. Fisher noted that, in 1936, Marinesco and Kreindler[14] had described a case of fleeting monocular blindness associated with carotid closure. In 1943, Andrell[2] reported a case in which there were "transient spells of blindness of the eye on the same side as the thrombosed internal carotid artery. It is noteworthy that this symptom retained its transient character in the face of the fact that the disease had otherwise attained a stationary stage." In his 1947 text, Walsh[20] reported a similar case (case 300 A). Of the 6 cases reported by Fisher[10], in 5 the loss of vision was never more than transient. In 3, the attacks ceased to occur after the stroke; in 1, they continued after the stroke; and in 1, they commenced only after the stroke. In the sixth case, episodes of transient monocular blindness occurred before the stroke; permanent blindness developed in this eye sometime after the stroke with the ophthalmoscopic picture of optic atrophy residual to previous closure of the central artery of the retina. In retrospect, 1 of the cases which I[18] reported in 1939 as an instance of amaurosis fugax with subsequent postspastic thrombosis of the central retinal artery may have represented really a thrombosis of the left internal carotid artery, since the patient had had transient right hemiplegia about 2½ months prior to occlusion of the central artery of the left retina. Case 514 in Walsh's[20] text may also belong to this group. Fisher[10] has said that intermittent monocular blindness may even be the only manifestation of occlusion of the internal carotid artery since in some cases occlusion does not result in hemiplegia.

Differentiation Between Occlusion of the Carotid and Occlusion of the Central Retinal Artery. In all the preceding cases, since the transient loss involved the entire visual field, the oph-

thalmic or the central retinal artery was evidently involved. In Fisher's[10] seventh case, loss of vision occurred only in the lower field. In spite of the presence of contralateral hemiplegia, Fisher was inclined to think that, in this patient, there might have been local disease of the ophthalmic or of the central retinal artery with an unrelated focus of hypertensive encephalomalacia. Hence, there is no definite proof as yet that thrombosis of the internal carotid can cause amaurosis fugax with involvement of a single retinal arteriole and only a sector of the visual field.

Fisher[10] said that in cases of amaurosis fugax, a possible differentiation between a causative atherosclerotic lesion in the central retinal artery and one in the internal carotid lies in the presence or absence of hypertension. He stated that "transient monocular blindness, occurring in older patients in the presence of hypertension, probably heralds the threatened occlusion of the central retinal artery, especially if pulsation in the internal carotid artery is good. Any subsequent hemiplegia is not directly related and means that a separate intracranial vessel has been occluded." He stated also that in cases in which occlusion of the internal carotid artery seems to be the fundamental process, the blood pressure is usually normal, pulsation of the carotid is absent and transient homolateral blindness and the onset of contralateral hemiplegia are closely related.

Fisher's[10] studies indicated that atherosclerotic plaques should appear in the central retinal artery only, or almost only, in the presence of hypertension. He noted that hypertension was present in all his own clinical cases of occlusion of the central retinal artery and in 13 of 15 cases of uncomplicated thrombosis of the central artery reported by Minton[15] (86%). Hypertensive disease is undoubtedly a factor in a high percentage of cases of closure of the central retinal artery or one of its branches. In 61% of a group of such cases tabulated from the files of the Mayo Clinic there was hypertension. The percentage of hypertensives was not quite so high in the previously mentioned group of 14 cases in which the histories were typical of amaurosis fugax. In only 6 of these (43%) did the patients have hypertension.

Classification of Reported Cases of Amaurosis Fugax. It is of some interest to know in what percentage of cases of amaurosis fugax permanent loss of vision may be expected to occur after a series of transient episodes. Fisher[10] collected from the literature reports of 138 cases of amaurosis fugax which he placed according to their presumed etiology in 7 groups: (1) cases in the older age group in which atherosclerosis was probably a factor; (2) cases in the younger age group without apparent cause; (3) cases associated with migraine; (4) cases associated with Raynaud's syndrome; (5) cases associated with heart disease; (6) cases of reflex amaurosis, such as those arising from irrigating the antrum or douching the vagina and (7) miscellaneous cases, including those which were difficult to classify on the basis of the data given. Permanent residual loss of vision was recorded in 16 of 34 cases in group 1 (47%); in 16 of 40 cases in group 2 (40%); in 15 of 24 cases in group 3 (63%); in 3 of 9 cases in group 4 (33%); in 2 of 7 cases in group 5 (29%); in 2 of 5 cases in group 6 (40%); in 4 of 19 cases in group 7 (21%); or in 42% of the entire group.

It would seem that the number of cases included in Fisher's[10] migraine group is disproportionately large. In 13 of the 24 cases included in his group 3, the etiologic relationship of migraine would seem to be doubtful. Fisher[10] himself in commenting on this group

says that "there are but a few unequivocal cases of unilateral blindness associated with migraine." It is probable that factors other than migraine were responsible for the loss of vision in at least some of these cases. In an extensive review of the ocular manifestations of migraine, Donahue[6] stated: "Unilateral blindness, transient amaurosis and obstruction or thrombosis of the retinal vessels have been described"; but he does not give any definite estimate as to the probable percentage frequency of such lesions. In general experience they would seem to be much less frequent than homonymous scintillating scotomas or hemianopsias. Among the 34 cases in group 1, there were 7 which Fisher[10] thought might well be instances of thrombosis of the internal carotid artery.

Assuming that spontaneous thrombosis of the internal carotid artery is the underlying cause for some cases of amaurosis fugax, yet recurring spasms in the central artery of the retina rather than in the diseased carotid artery seem best to explain the episodes of transient loss of vision. For, as Fisher[10] pointed out, if transient occlusion of the carotid artery accounted for the blindness, then transient blindness, hemiplegia, aphasia and paresthesia should all occur in the same episode rather than at different times. It seems unlikely that extension of the thrombus into the ophthalmic artery as described by King and Langworthy[13] would cause only transient loss of vision. In a personal communication to Fisher[10], Adams suggested that the blindness might be caused by spasm of the external carotid branches which had collateralized with the ophthalmic artery to supplement the inadequate supply through the internal carotid. But it seems more logical to assume that irritative spasm of vessels distal to a focus of organic vascular disease is the cause of most cases of amaurosis fugax, including those associated with thrombosis of the internal carotid artery. The presence of a local atherosclerotic plaque in an internal carotid artery might possibly explain the repeated initiation of episodes in some cases of amaurosis fugax by a particular movement of the head and neck.

Summary and Comment. Repeated episodes of sudden though transient loss of vision, even if only a portion of the visual field is involved, usually alarm the individual sufficiently to cause him to consult an ophthalmologist. Recurrent blurring of vision is of course a rather frequent complaint of eye patients. Recurrent actual loss of all or a part of the field of vision is complained of less frequently but still more often than would be suggested by the number of reports in the literature.

Often it is difficult, in the presence of normal vision and normal ocular fundi, for the ophthalmologist to determine from the history alone the exact nature of the attacks of which the patient complains. Usually, however, a patient who has amaurosis fugax in the restricted sense of angiospastic amaurosis fugax gives a readily recognizable story of the characteristic episodes. Repeated attacks of loss of vision which are described as complete in all or in a portion of the visual field, which persist for more than 10 minutes and which are then followed by recovery without evident residual should probably not be considered to be caused by ischemia of the retina unless spastic constriction of the arterioles can be actually observed during an attack. When the loss of vision is said to have persisted for a longer period than this, especially for several hours or days, with subsequent complete recovery, the suspicion of a functional basis for the complaint is always aroused. For instance, Abadie's[1] case, included by Fisher[10] in his miscellane-

ous group, is more suggestive of hysteria than of arterial spasm. It is true that some patients with typical migraine claim that loss of vision continues during the entire duration of the headache which may be for several hours or even a day or more. However, such cases are exceptional and in them the functional element cannot be entirely excluded. It must be remembered also that in some cases of acute retrobulbar neuritis, as in multiple sclerosis, the patient can recover rapidly with little or no ophthalmoscopically visible residual. However, retrobulbar neuritis seldom, if ever, recurs sufficiently often to give rise to a complaint suggesting amaurosis fugax.

In a patient with a history typical of the angiospastic type of amaurosis fugax, seen before any permanent residual is present in the vision or in the retina, it is important to discover, if possible, the cause of the recurrent spasms. However, in many cases, particularly in those in the younger age groups, the etiology remains obscure in spite of extensive investigations. Fisher's[9,10] intriguing observations indicate that, in all such cases, it should be noted whether pulsation is present in the internal carotid arteries and whether it is equal on the two sides. Should further studies tend to confirm Fisher's[9,10] views, which cannot be considered to be definitely proved as yet, it is possible that arteriographic examinations might be justified in all cases of amaurosis fugax.

Unfortunately, as yet, no satisfactory treatment for amaurosis fugax has been devised. Mild sedation may tend to diminish the frequency of the attacks as it seems to do in cases of central angiospastic retinopathy. Vasodilator drugs may be of value if given at the onset of the attack. Since both lowering of cerebral or retinal blood pressure and spastic arterial or arteriolar constriction may play a part in those cases in which, in a particular attack, the loss of vision persists for a longer time than usual, vasodilator drugs are helpful only if they are used in dosage insufficient to cause a significant drop in blood pressure. It has not been demonstrated as yet that block of the stellate ganglion is uniformly effective in preventing or relieving spastic constriction of the central artery of the retina or of the retinal arterioles.

REFERENCES

(1) **Abadie, C.**: Quoted by Fisher, Miller[10]. (2) **Andrell, P. O.**: Acta med. Scandinav., **114**, 336, 1943.
(3) **Behrman, S.**: Arch. Ophth., **45**, 458, 1951.
(4) **Coston, T. O.**: Am. J. Ophth., s. 3, **34**, 1289, 1951.
(5) **Davenport, R. C.**: Tr. Ophth. Soc. U. Kingdom, **51**, 115, 1931. (6) **Donahue, H. C.**: Tr. Am. Ophth. Soc., **47**, 554, 1949. (7) **Duke-Elder, W. S.**: Text-book of Opthalmology; Disease of the Inner Eye. St. Louis, The C. V. Mosby Company, 1940, vol. 3, 3,470 pp.
(8) **Engel, G. L., Ferris, E. B., Jr.,** and **Romano, John**: Am. J. M. Sci., **209**, 650, 1945.
(9) **Fisher, M.**: Arch. Neurol. & Psychiat., **65**, 346, 1951. (10) Idem: Arch. Ophth., **47**, 167, 1952.
(11) **Graveson, G. S.**: Brit. Med. J., **2**, 838, 1949. (12) **Grönvall, H.**: Acta ophth., **16**, 602, 1838.
(13) **King, A. B.,** and **Langworthy, O. R.**: Arch. Neurol. & Psychiat., **46**, 835, 1941.
(14) **Marinesco, G.,** and **Kreindler, A.**: Presse Méd., **1**, 833, 1936. (15) **Minton, J.**: Proc. Roy. Soc. Med., **30** (pt. 1), 285, 1936-1937.
(16) **Pal, J.**: Med. Klin., **25** (pt. 1), 702, 1929.
(17) **Rosenstein, A. Maria**: Klin. Monatsbl. f. Augenh., **75**, 357, 1925.
(18) **Wagener, H. P.**: Tr. Pacific Coast Oto-Ophth. Soc., **24**, 165, 1939. (19) **Wagener, H. P.,** and **Gipner, J. F.**: Am. J. Ophth., **10**, 650, 1927. (20) **Walsh, F. B.**: Clinical Neuro-ophthalmology. Baltimore, Williams & Wilkins, 1947, 1,532. pp.

BOOK REVIEWS AND NOTICES

ENGLISH-GERMAN MEDICAL DICTIONARY. By F. S. SCHOENEWALD, M.D. Pp. 242. Philadelphia: The Blakiston Co., 1951. Price, 6.00.

THIS is a companion volume to the German-English Medical Dictionary recently published. It is planned to supply the two books separately, but if there be sufficient demand they may eventually be issued in a single volume. The author, who was educated and lived much of his life in Germany, went to England in the 1930's and became completely bilingual. He read 30,000 pages of Anglo-American medical literature and translated all the words into German, and this material was the basis for the German-English dictionary. The German words then were readjusted to the original English words and became the basis of the second volume. It is noteworthy that there are included not only purely medico-technical terms but those words of lay language commonly used in medical practice and literature to describe, explain and discuss matters of health and disease. A particularly valuable aspect of the book is the use of words in sentences to illustrate shades of meaning. It is really a phrase dictionary, not simply a glossary. The author unfortunately died before the appearance of the last volume but his son-in-law, also bilingual, saw it through the press. The book is heartily recommended. R. K.

WHEN DOCTORS ARE PATIENTS. Edited by MAX PINNER, M.D., and BENJAMIN F. MILLER, M.D. Pp. 364. New York: W. W. Norton & Co., 1952. Price, $3.95.

IN this remarkable book, 33 physicians, including the two editors, tell of their own experiences with a severe or serious illness and disability, and how they reacted and became adjusted thereto. All of them men of attainment in the profession, most of them teachers and gifted in the art of communicating their knowledge, they have brought within the limits of this volume a wealth of self-analysis and medical self-experience that stands unrivaled in medical literature. Their ailments include various forms of cardiac disease; the handicaps of blindness, deafness and the residual paralysis of poliomyelitis; the pains of kidney stone, migraine and dengue; addictions to morphine and to alcohol; adaptation to overwhelming disease such as multiple sclerosis, cancer of both breasts, and manic-depressive psychosis; chronic infections and allergic disorders, such as bronchitis, tuberculosis, brucellosis and rheumatoid arthritis; personal achievements in diagnosis and treatment, as exemplified in epilepsy, narcolepsy and hypertension; the gains and losses from advancing years. Some of the writers have chosen to be anonymous. Some are well known to most physicians. The breadth of the appeal of many of the articles is attested by the pre-publication of some of the chapters in the Atlantic Monthly. The editors have done the medical profession and the world at large a signal service. The book should be read by every physician. R. K.

DER EINFLUSS DES NERVENSYSTEMS AUF BAU UND TATIGKEIT DER GESCHLECHTSORGANE DES MENSCHEN. By Prof. Dr. Med. et Phil. H. STIEVE. Pp. 191; 93 ills. Stuttgart, Germany: Georg Thieme Verlag, 1952. Price, DM 36.

THE material presented in this book includes a survey of normal anatomy and physiologic activity of both ovary and testes and the alteration in their function due to anxiety and psychologic trauma. For the most part the presentation is devoted to the ovary and uterus, only one chapter concerning the testes. The author suggests that psychic trauma can halt both testicular and ovarian activity, thus interfering with male and female fertility and with the menstrual cycle in the female. The older the woman at the time of the psychic shock the more permanent may be the effect. For instance in the late 30's the ovaries may be so affected that they cannot recover and premature menopause results. Complete suppression of activity is less common in young women. An interesting suggestion is that more abnormal infants are produced by older women because the ovaries recover less completely from such shocks and produce abnormal ova; in addition the longer the period of psychic amenorrhea the more likely is an abnormality to occur should the patient become pregnant.

The book is well written and adequately documented with case material. The illustrations are excellently reproduced but are often repetitious. This presentation should be of particular interest to gynecologists and

endocrinologists who are called upon to deal with the problems of menstruation and ovarian dysfunction discussed. J. W.

DIE TRANSFUSION VON KONSERVIERTEM BLUT IN DER GEBURTSHILFE UND GYNÄKOLOGIE. By PROF. DR. H. SCHWALM, University of Marburg, (Lahn) Germany. Pp. 132; 21 ills. Stuttgart, Germany: Georg Thieme Verlag, 1952. Price, DM 14.70.

THE monograph discusses in detail the use of whole blood and plasma in obstetrics and gynecology.

The first portion deals with indications for and contraindications against blood transfusion in both women and newborn infants and in general agrees with the approach to fluid replacement in this country. The source of blood for transfusion is next considered and in addition to blood donors transfusion with infant cord blood and blood recovered from the peritoneal cavity after hemorrhage is discussed. Techniques for the collection and preservation of blood and the prevention of changes during storage are carefully outlined. Methods of administration are presented in detail and the prevention, detection and management of reactions is discussed. The use of serum, plasma and cell concentrations is clearly outlined.

This is an excellent discussion of blood transfusion, containing a large amount of important information of historical, scientific and practical nature and should be a valuable aid in setting up a blood transfusion service. J. W.

MEDICAL DIAGNOSIS, APPLIED PHYSICAL DIAGNOSIS. Edited by ROSCOE L. PULLEN, M.D. 2nd ed. Pp. 1,119; 601 ills., 48 in color. Philadelphia: W. B. Saunders Co., 1950. Price, $12.50.

THE pattern of this text is highly commendable. Instead of an over-emphasis on heart and lungs, there is coverage of the whole patient. Instead of concerning itself solely with physical diagnosis, the book begins with history taking, and also includes other diagnostic procedures, such as endoscopy, electrocardiography, Roentgen examination and histological findings. The arrangement is by body regions and with attention to diseases as they predominantly affect the structures of the region. Although the coverage is at times rather thin, the end result is nevertheless a most valuable book, on which the editor and his 22 associate authors are to be complimented. There are numerous illustrations, most of which are excellent, a few are too small. This second edition has improved on the first by the addition of chapters on The Bedside Diagnosis of Blood Diseases, Medical Diagnosis in the Aged, and The Physical Examination of the Psychotic Patient. The book is highly recommended. R. K.

VIRUS AND RICKETTSIAL DISEASES. By S. P. BEDSON, M.D., A. W. DOWNIE, M.D., F. O. MACCALLUM, M.D., and C. H. STUART-HARRIS, M.D. Pp. 383; 33 ills. Baltimore: Williams & Wilkins Co., 1950. Price, $5.50.

AN excellent survey of current knowledge of viral and rickettsial diseases. The clinical descriptions have been limited to a bare outline, with emphasis rather on the etiological point of view, the character of the viruses, the practical aspects of epidemiology and control, and the diagnostic aid which the laboratory can give the clinician. This brief readable text will be welcomed by the profession. R. K.

PEDIATRIC ALLERGY. By ROBERT CHOBOT, M.D., Dir. Pediatric Allergy Clinic, N. Y. Univ.—Bellevue Med. Center. Pp. 284. New York: McGraw-Hill, 1951. Price, $4.50.

THE author, on the basis of his extensive experience in the field, has produced a text on the clinical aspects of allergy in children which the pediatrician and general practitioner will find very useful. He has avoided unnecessary detail of theoretical aspects. The style is vivid and reflects the enthusiasm of the writer. In trying to be terse he has, at times, been more dogmatic than accurate as when he says that "all house dust seems to have a common excitant," or that "horse hair (properly cleaned and sterilized) can be used in pillows and mattresses with impunity." The fact remains that the book is extremely practical and its value is enhanced by numerous illustrative case reports. R. K.

A CLASSIFIED BIBLIOGRAPHY OF GERONTOLOGY AND GERIATRICS. By NATHAN W. SHOCK, M.D., Chief, Section on Gerontology, National Heart Institute. Pp. 599. Stanford, Calif.: Stanford University Press, 1951. Price, $15.00.

THE importance of an interest in the problems of aging and of the aged has increased at a rate and to a degree that can best be appreciated by this compilation of over 18,000 references to publications in the field; most of which have appeared in the last decade.

This bibliography is indispensible to all interested in gerontology. It should be on the shelf of every medical library. A program for future supplements is already under way.

R. K.

TRENDS IN GERONTOLOGY. By NATHAN W. SHOCK, Chief, Section on Gerontology, National Heart Institute. Pp. 153; 12 ills. Stanford, Calif.: Stanford University Press, 1951. Price, $2.50.

THIS little volume contains much important information in the field of gerontology. Chapter headings are revealing: Trends in Population, in Employment, in Income Maintenance and Retirement, in Health Maintenance, in Living Arrangements, in Education, in Community Programs for the Aged, and in Research. Of practical interest are the chapters on Research Potentialities and Methods of Furthering Research in Gerontology. The author proposes the founding of an "Institute of Gerontology" to foster and execute research programs on aging: its biology, its physiological and psychological aspects, its clinical problems and its socio-economic problems.

R. K.

THE PHOTOGRAPHY OF PATIENTS. By H. LOU GIBSON, F.B.P.A., A.P.S.A., Medical Division, Eastman Kodak Co., Rochester, N. Y. Pp. 118; 42 ills., and 4 color plates. Springfield, Ill.: Charles C Thomas, 1952. Price, $5.50.

THE value of photography in medicine is increasing rapidly as an important means of recording clinical and pathological material and as a means of presenting that material in teaching. This little book, prepared by a member of the Medical Division of the Eastman Kodak Company, is full of practical information for the amateur photographer but without going into unnecessary and abstruse detail. It is highly recommended.

R. K.

COMMUNICABLE DISEASES. Edited by ROSCOE L. PULLEN, M.D. Pp. 1,035; 235 ills., 35 in color. Philadelphia: Lea & Febiger, 1950. Price, $20.00.

THIS book offers a new approach to medical practice in the management of the communicable diseases. The great advances in chemotherapy of recent years have changed both the progress of disease in the individual patient as well as the considerations of epidemiology and treatment. It has been possible, therefore, to revise concepts of isolation techniques and to consider the possibility of handling of certain diseases on general hospital wards or in the home. Fifty-three contributing authors, all of them authorities in their fields and most of them teachers of medicine, have produced a book of great practical value. The numerous illustrations, many of them in color, are exceedingly well done. The book is highly recommended not only to teachers and students but to general practitioners as well.

R. K.

DIFFERENTIAL DIAGNOSIS OF INTERNAL DISEASES. By JULIUS BAUER, M.D., Clin. Prof. Med., College of Medical Evangelists. Pp. 866; 55 ills. New York: Grune & Stratton, 1950. Price, $12.00.

THIS book is an interesting presentation of the differential diagnosis of internal diseases, by considering a number of major symptoms and signs. In the first section, the author discloses the causes of headache, chest pain, abdominal pain, backache, pain in the extremities, disorders of general feelings, disorders of consciousness; vertigo, nausea and vomiting; paralysis and disturbances of movements; cough and dyspnea; diarrhea and constipation; hemorrhages. The second section deals with major signs as related to the general appearance, to fever and infections, and to the respiratory, cardiovascular, digestive, hemopoietic and uropoietic systems; and glycosuria. There is, unfortunately, practically no coverage of signs or symptoms referable to the hands and eyes. The material and mode of presentation are excellent, reflecting the broad knowledge and practical viewpoint of the author. The style is vivid, with a European flavor that leans to greater use of Latin terms and, at times with a different shade of meaning than is here current (vomitus for vomiting). Better printing, with the use of bold face type in addition to italics, would greatly enhance the availability of the information. In its present form it makes good continuous reading but is not readily available for quick reference.

R. K.

MODERN PRACTICE IN INFECTIOUS FEVERS. Edited by H. S. BANKS. Pp. 1,054; 211 ills. New York: Paul B. Hoeber, Inc., 1951. Price, $20.00.

THIS two-volume work on the Infectious Fevers is a publication of major importance in this field. Its 52 contributions come from the British Isles, the United States, France, Egypt, South Africa, India and Australia, and are authorities in their respective fields. The first volume deals with general practice: Ecology and Epidemiology; Laboratory Aids

to Diagnosis and Treatment; all aspects of Immunization; the Clinical Use of Antibiotics; then follow sections covering the various Bacterial Diseases. Volume 2 includes the discussions of the Viral Fevers, the Rickettsial Diseases, certain Spirochetal Fevers; Protozoal Infections, Mycotic Fevers and Infections of Unknown Etiology. The coverage in these several fields is for the most part adequate and world-wide in its scope. It is in some of the tropical conditions that there are gaps. There is no mention of yaws, bejel, pinta or mucocutaneous leishmaniasis. The article on malaria is rather sketchy and there is no mention of Camaquine in its treatment. Primaquine has, of course, appeared since the book went to print. Except for tuberculous meningitis, there is no mention of tuberculous infection, and there is no mention of syphilis. Since chapter headings all refer to "Fevers," it may be that more chronic processes were omitted. The format and arrangement of the book are highly commendable. The text material is made easily available by good sub-headings. The illustrations are excellent. The bibliography is adequate. The work should receive wide approval. R. K.

Der Ultraschall in der Medizin, Band 2. Fortschritte auf biologischem und medizinischem Gebiet unter Berucksichtigung der Ergebnisse des internationalen Ultraschall Kongresses 1950 in Rom. Edited by Karlheinz Woeber. Pp. 71; 3 ills. Zürich: S. Hirzel, 1950. Price, not given.

A summary of advances in the field of ultrasonics in medicine, as reported at the International Ultrasonic Congress in Rome, 1950. It will be found of interest to those able to read German. R. K.

Conference on Problems of Aging. Edited by Nathan W. Shock, Chief, National Heart Institute. Pp. 194; 24 ills. New York: J. Macy, Jr., Foundation, 1951. Price, $4.00.

This is a verbatim report of six papers presented at the 13th Session of the Conference on Problems of Aging together with the discussions by various members of the conference and invited guests. R. K.

Studies in Medicine: A Volume of Papers in Honor of Robert Wood Keeton. Pp. 396; illustrated. Springfield, Ill.: Charles C Thomas, 1951. Price, $8.50.

The friends and associates of Dr. Robert Wood Keeton prepared this volume in his honor on the occasion of his retirement as Head of the Department of Medicine at the University of Illinois College of Medicine, August, 1951. The 33 chapters, prepared by 58 contributors, cover a wide range of subjects that testify to Dr. Keeton's manifold interests as well as to the attainments of the men whose activities he inspired. R. K.

Clnical Allergy. By Samuel J. Taub, M.D. 2nd ed. Pp. 276. New York: Paul B. Hoeber, Inc., 1951. Price, $4.50.

In this second edition of this book, the author adheres to his purpose of giving a simple and concise presentation of the field of allergy for the general practitioner and the medical student. The value of the book would, however, have been enhanced by some references to important sources and publications rather than the actual mention in the text of only a worker's last name. R. K.

American Journal of Tropical Medicine and Hygiene, Volume 1, No. 1. Pp. 175; ills. Baltimore: Williams & Wilkins Co., 1952.

This is the first issue of the American Journal of Tropical Medicine and Hygiene which takes the place of two former publications, the American Journal of Tropical Medicine and the Journal of the National Malaria Society. The new journal is more comprehensive than either of the old in the range of its interests and should, therefore, have a wider appeal and usefulness. The first number is a commemorative issue in honor of Dr. Charles Franklin Craig, a pioneer and leader in this field. The sponsors and editors of the new publication are to be congratulated and have the best wishes and acclaim of the many physicians in this country and abroad who are interested in this important phase of medicine. R. K.

Visceral Innervation and Its Relation to Personality. By Albert Kuntz, M.D., Ph.D. Prof. of Anatomy, St. Louis Univ. Sch. of Med. Pp. 152; 31 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $4.50.

In this excellent monograph, Dr. Kuntz gives a detailed review of the anatomy of the autonomic nervous system and its functional interrelations with somatic nerves and the

endocrine system. The visceral nerves are considered in relation to autonomic reflex and integrating centers of the central nervous system. Under general physiology, many of the bodily activities are discussed. The actions of cholinergic and adrenergic nerves are explained and the interrelations between these functional types of nerves and the endocrine system are outlined. The fiber connections between the hypothalamic (autonomic) centers and other parts of the nervous system are reviewed. Based on these connections, and the function of the olfactory cortex, the autonomic nervous system is discussed in relation to personality.

Dr. Kuntz is an outstanding leader in the field of neuroanatomy. His many contributions to our knowledge of the autonomic nervous system are well known. His monograph is a valuable contribution to medical literature. D. K.

RENAL PELVIS AND URETER. By PETER A. NARATH, M.D., F.I.C.S., Adjunct Prof. of Urol., New York Polyclinic Med. Sch. and Hosp. Foreword by Joseph F. McCarthy, M.D. Pp. 428; 264 ills. New York: Grune & Stratton, 1951. Price, $12.50.

THE monograph presents in a concise manner an interpretation of fundamental principles of the normal anatomical configuration and function of the renal pelvis and ureter. Variations of the normal as related to a pathological state are well summarized and discussed. The material of the text is presented in a logical sequence. An extensive bibliography is given. A cross index of authors and subjects is well formulated. All these enhance the value of the book as a reference.

The paper is of good quality and the type is good to permit easy reading.

The book is recommended to those interested in the anatomy, physiology and dynamics of the upper urinary tract. L. M.

A TEXTBOOK OF MEDICINE. Edited by E. NOBLE CHAMBERLAIN, M.D., M.Sc., F.R.C.P., Senior Lecturer in Med., Univ. of Liverpool. Pp. 962; 266 ills. Baltimore: Williams & Wilkins, 1951. Price, $10.00.

WRITTEN by a group of 17 British physicians, this textbook of medicine is designed to select for the medical student the knowledge which is of most importance for him to use along with his practical hospital experience. The plan has been to lay emphasis on the salient features of disease and to limit the description of the rarity. Treatment has been dealt with on general principles rather than in great detail.

The Reviewer is impressed, however, with a general brevity of presentation which would be totally inadequate for medical students in most schools, and most certainly for those in their junior and senior years. There has been a laudable emphasis upon oft-neglected psychological medicine and upon occupational diseases and toxicology, but the reader wonders about proper balance when he notes 4 photographs of acromegaly and 2 color prints of Cushing's disease and yet but one line of reference to the very common condition, postmenopausal osteoporosis, and that under the heading of Osteomalacia, the impression being given that response would be obtained by means of vitamin D and calcium therapy! Lupus erythematosus is mentioned nowhere in the book.

Dicumarin therapy is covered in one sentence under disorders of the clotting mechanism and is named in the treatment of thrombophlebitis, but not in myocardial infarction. Nothing is said regarding dangers involved nor of the need for careful control. The extremely rare Charcot's arthropathy rates 2 photographs, and yet ventricular tachycardia is only barely mentioned! Many more examples could be cited, but it appears obvious to the Reviewer that a satisfactory textbook of medicine cannot be condensed into 962 large print pages measuring 6 by 9 inches, especially when rare entities have not been sufficiently reduced in emphasis. T. D.

DISEASE IN INFANCY AND CHILDHOOD. Edited by RICHARD W. B. ELLIS, M.D., F.R.C.P. Prof. of Child Life and Health, Univ. of Edinburgh; Physician, Royal Hosp. for Sick Children, Edinburgh; formerly Physician in charge of the Children's Dept., Guy's Hospital, London. Pp. 695; 300 ills. Baltimore: Williams & Wilkins, 1951. Price, $13.50.

THIS volume is eminently suitable for the general practitioner, more so perhaps than for the specialist in pediatrics. The field is surveyed concisely but comprehensively, including such special topics as history taking, constitutional influences, growth disorders, social factors, and behavior problems. The discussions of the various diseases are concise but adequate, and are up-to-date with respect to diagnostic features and therapeutic procedures. The subject matter has been thoughtfully organized, usually according to organ systems. Anatomic malformations are extensively surveyed, and the chapter on tuberculosis is particularly informative. I. W.

A TRANSLATION OF GALEN'S HYGIENE (De Sanitate, Tuenda). By ROBERT MONTRAVILLE GREEN, M.D., Emeritus Prof. of Anat. Harvard Medical School, with an Introduction by H. E. SIGERIST, M.D. Pp. 277. Springfield, Ill.: Charles C Thomas, 1951. Price, $5.75.

IT is indeed strange that the man who dominated medical thought for more than a thousand years should not have had his *Opera* and more than a very few of his individual works translated into a modern language. The very bulk of his writings, to be sure, militates against translations just as the completeness of the domination of his precepts not only hindered progress but flared back to the detriment of his standing in the light of modern concepts. For Galen was not only the outstanding practitioner of his time but also an acute observer, an able investigator, and a pioneer experimenter in the fields of anatomy, physiology, and applied pharmacology. As Sigerist points out in a charming Introduction, Galen's works are also valuable as a huge repertory of ancient medical literature, a fact of added importance in view of the total loss of all important medical works written between the Hippocratic Corpus and Galen's own works. And this hiatus covering a period when the Roman Republic and Empire were in finest flower and the Alexandrian School attaining new scientific heights.

When all has been said, however, the text of this work on hygiene contains but little sound meat. The domination of the concept of the humors in health and disease, requiring that all phenomena and therapy be explained or advocated on this basis, makes most of the exposition meaningless to modern eyes. The text, then, has its value indirectly as an indicator of the biological line of thought that exerted such lasting influence. It appears to have been carefully and competently translated and makes at least a good step toward the desirable goal of putting Galen's writings in a form usable by modern students of our medical past. E. K.

THE SPECIALTIES IN GENERAL PRACTICE. Edited by RUSSELL L. CECIL, M.D., Prof. of Clin. Med., Emeritus, Cornell Uni. Med. Coll., New York City. Pp. 818; 470 ills. Philadelphia and London: W. B. Saunders Co., 1951. Price, $14.50.

THAT the family doctor should be returned to his old established place in the practice of medicine is recognized by everyone. With the rapid advances which have been made in the medical specialties, however, it is difficult for him to keep his practice up-to-date in every field, and he further finds that the specialty texts which he consults are mainly written by specialists *for* specialists. Dr. Cecil is to be congratulated, therefore, for having conceived the idea of this splendid volume, and for having achieved the editorial triumph of a book written *for* the general practitioner, giving him just what he needs in each particular special field.

Fourteen distinguished contributors have provided chapters which deal with minor surgery, orthopedic surgery, fractures and dislocations, urology, proctology, gynecology, obstetrics, pediatrics, ophthalmology, otorhinolaryngology and bronchoesophagology, dermatology and syphilology, and psychiatry. Each of these contributors has succeeded admirably in providing for the everyday problems of the doctor located in areas where early consultation with the specialist is not feasible. He is also aided in early recognition of conditions which require the aid of the specialist, and the part which he can play in rehabilitation following return from the specialist is stressed where indicated. This book fills a very real need and should be of great value to every general practitioner who is anxious to practice up-to-date medicine and surgery. T. D.

POST-GRADUATE LECTURES ON ORTHOPEDIC DIAGNOSIS AND INDICATIONS, VOLUME III. By ARTHUR STEINDLER, M.D., F.A.C.S., Prof. of Orth. Surg., State Univ. of Iowa. Pp. 270; 372 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $8.75.

THIS third volume by Dr. Steinler compares most favorably with Volumes I and II. In his latest text, Tuberculosis of the Skeletal System and Osteomyelitis, are the topics under discussion, and one should add, ably.

From the number of illustrations, the detail and clarity of presentation, it is most apparent that the author has a complete grasp of his subject. It is a text that can be unconditionally recommended to anyone interested in bone and joint disease. A. S.

KLINISCHE ELEKTROKARDIOGRAPHIE. By DR. MAX HOLZMANN, Zurich, Switzerland. 2d ed. Pp. 652; 302 ills. Stuttgart: George Thieme Verlag, 1952. Price, DM 69.60.

THE first edition was translated into Italian and Spanish and of the second edition a translation into English is announced. The Anglo-American and French literature is

very adequately covered. The theory and physiologic aspects, including a detailed presentation of vector analysis of the electrocardiogram are very adequately presented. Abnormal electrocardiograms are discussed under the following headings: technical errors; situs inversus; fixation of the heart; abnormal amplitudes; abnormal findings with respect to the atrial and ventricular portion, including the length of the electrical systole; preponderance; inflammatory, toxic, allergic, endocrine and vitamin disturbances; primary myocardial alterations; the influence of digitalis; ischemia—coronary insufficiency—infarction group; pericarditis; pulmonary embolism; orthostatic and neuro-vegetative effects. The subsequent presentation of the disturbances of rhythm includes valuable therapeutic remarks. There follow discussions of the W-P-W syndrome and of the electrocardiographic findings in trauma of the heart, in systemic diseases of the neuro-muscular system, and finally in the dying heart.

Detailed electrocardiographic analysis and evaluation is always well tempered by the author's mature clinical judgment. The value of a number of case presentations is enhanced by giving the post mortem data.

The line drawings are very instructive and technically superb. The publisher deserves high commendation for the excellency of both the printing and the reproduction of the photographic material. The quality of reproduction depends upon a number of factors—paper, ink, speed of printing process and last, but not least, fineness of the screen—and the reproductions in many medical books and journals in our country could be remarkably improved if we could persuade the publishers to use finer screens in spite of the slightly higher cost involved. The reviewer stresses this point because few medical authors and editors seem to be aware of the technical procedures involved in reproducing scientific illustrations and, therefore, cannot effectively exert pressure on publishers to improve the quality of illustrations. H. R.

JOLL'S DISEASE OF THE THYROID GLAND. By FRANCIS F. RUNDLE, M.D., F.R.C.S. 2d ed. Pp. 520; 165 ills. New York: Grune & Stratton, Inc., 1951. Price, $12.75.

THIS is an excellent book for medical students and general practitioners alike. It is well organized and lucidly written with informative figures and charts. Of particular value is the section on Thyroid Physiology which is well illustrated with pertinent figures. A large section is devoted to the surgical technique of the thyroid gland which will be of little interest to many readers. As is so often the case with textbooks concerning the thyroid gland, the section on hypothyroidism is completely inadequate consisting of only one page of discussion. W. P.

NUTRITION AND CLIMATIC STRESS WITH PARTICULAR REFERENCE TO MAN. By H. H. MITCHELL, Prof. of Animal Nutrition, and MARJORIE EDMAN, Research Assistant in Animal Nutrition in Charge of Literature Survey, Univ. of Ill. Pp. 244; 8 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $6.75.

THE need for attaining greatest possible military efficiency under conditions of unusual climatic stress led, during World War II, to considerable research into various factors involved in adaptation to such stress. The purpose of this volume is, first, to cover thoroughly and critically those experiments and observations dealing directly with the relationships of nutrition and climatic stress, namely, the effect of climatic stress on nutritional requirements, and the effect of the food supply upon tolerance to such stress; and, second, to discuss the background information, bearing indirectly, and perhaps only remotely, upon the nutrition-environmental stress theme. This is done under three headings: (1) diet in a cold environment; (2) diet in a hot environment; and (3) diet at altitude. The book is well written and contains a great store house of material which is of interest to nutritionists and to all those dealing with climatic adaptation. T. D.

NEW BOOKS

Cellular Changes with Age. By WARREN ANDREW, PH.D., M.D., Prof. of Anat., George Washington Univ. School of Med. Pp. 74; 25 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $2.50.

THIS little monograph gives a brief summary of cellular changes as observed not only in man and other mammals but in lower vertebrates, invertebrates and plants in the process of aging. The illustrations are excellent and there is a good bibliography. Pathologists will be particularly interested in this work. R. K.

Your Questions Answered. Edited by HUGH CLEGG. Pp. 240. New York: Grune & Stratton, Inc., 1951. Price, $2.50.

FROM the department, "Any Questions" of the British Medical Journal, the Editor of that publication has selected 192 questions and their answers, ranging from a few lines to a page or two, and touching on all fields of clinical medicine. R. K.

Pasteur's Study of Fermentation. Case 6 of Harvard Case Histories in Experimental Science. Edited by JAMES BRYANT CONANT. Paperbound. Pp. 57. No illustrations. Cambridge: Harvard Univ. Press, 1952. Price, $1.00.

THIS series of "Case Histories", designed primarily for students majoring in the humanities or social sciences, aims to give them an understanding of science by acquiring "a detailed knowledge of a few epoch making advances". Such a one is "Case 6", Pasteur's study of fermentation, which opened new fields in several branches of science, especially in the causes and treatment of infectious diseases.

E. K.

Biologisch-Medizinisches Taschenjahrbuch, 1952. Edited by DR. MED. HANS HAFERKAMP. Pp. 583. Stuttgart: Hippokrates-Verlag, Marquardt & Cie, 1952. Price, DM 7.50.

Refraction Correlated with Optics and Physiological Optics and Motility Limited to Heterophoria. By WALTER B. LANCASTER, M.D. Pp. 310; 99 ills. Springfield, Ill.: Charles C Thomas, 1952. Price, $7.75.

Thomas Jefferson: Scientist. By EDWIN T. MARTIN, Professor of English, Emory University, Georgia. Pp. 289; 15 ills. New York: Henry Schuman, Inc., 1952. Price, $4.00.

AN interesting portrayal of one aspect, little known by most people, of the many-sided man who is remembered primarily as a statesman, politician, drafter of the Declaration of Independence and the Third President of the United States. Physicians and other scientists will find much of interest in this book.

R. K.

Control and Removal of Radioactive Contamination in Laboratories. National Bureau of Standards Handbook 48. Pp. 24. Washington, D. C.: U. S. Department of Commerce, 1952. Price, $.15.

X-Ray Calibration of Radiation Survey Meters, Pocket Chambers, and Dosimeters. NBS Circular 507. National Bureau of Standards. Pp. 11; 11 fig. Washington, D. C.: U. S. Department of Commerce, 1952. Price, $.15.

THESE two little books, both published by the National Bureau of Standards, follow the pattern of prior handbooks and circulars in the field of radiation physics, in presenting concise and authoritative recommendations for the handling and use of radioactive materials and associated instruments.

R. R.

Pencillin Decade. By L. W. SMITH, M.D., Medical Director of Commercial Solvents Corporation, and A. D. WALKER, R.N., Former Editor of "Trained Nurse and Hospital Review." Pp. 122. Washington, D. C.: Arundel Press Inc., 1951. Price, $2.50.

THE authors have made an intensive and detailed review of the available literature of the past decade concerning the untoward effects of pencillin therapy; they have reviewed and abstracted some 342 articles; and have stressed that more caution should be exercised in the administration of pencillin and other antibiotic agents.

C. B.

Isotopes in Biochemistry. Edited for the Ciba Foundation by G. E. W. WOLSTENHOLME. Pp. 303; 79 ills. Philadelphia: The Blakiston Company, 1951. Price, $5.00.

A report on the Ciba Foundation conference, held March 12-15, 1951, in which participated many outstanding workers in the field. Papers read included three or four under each of the following topics: steroids, hemoglobin and metabolic derivatives, use of tracers in the study of biological effects of radiation, nucleic acids, proteins and amino acids carbohydrate and fatty acid metabolism. Each of the 22 papers is accompanied by a verbatim report of the discussion which followed its presentation.

R. H.

Biological Antioxidants. Edited by COSMO G. MACKENZIE, Department of Biochemistry, University of Colorado School of Medicine. Pp. 229; 32 fig. New York: Josiah Macy, Jr. Foundation, 1951. Price, $3.75.

TRANSACTIONS of the Fifth—and last of the series — Conference November 30-December 1, 1950, New York. Contents: Chemical changes produced by radiations, Robert S. Livingston; general introduction to radiation effects on higher animals, Austin M. Brues; effect of ionizing radiations on sulfhydryl systems, E. S. Guzman Barron; genetic effects of irradiation and irradiated broths, Orville Wyss; peroxides and mutations, Frank Dickey; free radicals, peroxides, and antioxidants in some biological processes, Elwood V. Jensen; cumulative index to conferences 1946-1950. Each paper followed by a verbatim report of the discussion that followed. A special effort has been made to keep the language as understandable as possible by scientists in other fields. Authoritative and interesting.

R. H.

Caelius Aurelianus Gynaecia. Edited by MIRIAM F. DRABKIN and ISRAEL E. DRABKIN. Supplement 13 to the Bulletin of the History of Medicine. Pp. 136; no ills. Baltimore: Johns Hopkins Press, 1951. Price, $3.00.

THESE fragments of a Latin version of Soranus' Gynaecia are from a 13th century manuscript which was offered for sale in 1948 by L'Art Ancien of Zurich and is now privately owned in Buffalo. It may be regarded as a supplement to Soranus' larger work edited by I. E. Drabkin that

was reviewed in these columns (A.J.M.S., 222, 611, 1951). E. K.

Allergic Pruritus. Edited by STEPHAN EPSTEIN, M.D. Pp. 76; 6 ills. St. Paul, Minn.: Bruce Publishing Co., 1952. Price, $2.50.

THIS is a collection of 7 papers by 9 authors presented at a Symposium on Itching Dermatoses presented in April, 1950, at the Annual Session of the American College of Allergists. R. K.

Cas Phäochromozytom. By PROF. DR. HEINRICH SACK. Pp. 93; 26 ills. Stuttgart: Georg Thieme Verlag, 1951. Price, DM 11.70.

THIS little monograph is a well-written summary of current knowledge about this important tumor. Those who read German will find it useful and instructive. R. K.

Trauma, Growth, and Personality. By PHYLLIS GREENACRE, M.D., Prof. of Clin. Psychiatry, Cornell Univ. Med. College. Pp. 328. New York: W. W. Norton & Co., 1952. Price, $4.50.

THIS book is a collection of papers, most of which have already appeared in various journals. They deal with various traumata of childhood and their effect upon personality development, particularly in relation to symptom formation. The theoretical material is liberally documented with case histories, which are clear, not too detailed and which convincingly portray the importance of early childhood experience in personality formation. The book is predominantly suited to the student and practitioner of Psychiatry. O. E.

The Present Status of Antibiotic Therapy with Particular Reference to Chloramphenicol, Aureomycin and Terramycin. By FRANCIS G. BLAKE, M.D., Dept. of Internal Medicine, Yale University School of Medicine. Pp. 26. Springfield, Ill.: Charles C Thomas, 1952. Price, $.90.

A concise and authoritative statement of the value of antibiotics, especially the three mentioned, in the treatment of scrub, epidemic and murine typhus; Rocky Mountain spotted fever, boutonneuse fever, rickettsial pox, Q fever, psittacosis, lymphogranuloma venereum, primary atypical pneumonia, typhoid fever, amebiasis, brucellosis, tularemia and whooping cough. R. K.

The Internship. By ROSCOE L. PULLEN, M.D., F.A.C.P., Prof. of Grad. Med., Tulane Univ. of La. School of Med. Pp. 35. Springfield, Ill.: Charles C Thomas, 1952. Price, $1.25.

A critical study of a problem of growing importance and complexity, it presents the factors influencing the internship, the educational adaptation of internships today, and the author's suggested modification of the internship. Medical educators and hospital administrators will find here material for thought and constructive discussion. R. K.

Hippocrates on Intercourse and Pregnancy. An English translation of *On Semen and on the Development of the Child.* By TAGE U. H. ELLINGER, Sc.D., M.A., with an introduction by ALAN F. GUTTMACHER, M.D., Pp. 128; no ills. New York: H. Schuman, 1952. Price, $2.50.

THIS, the first English translation of one of the books of the Hippocratic Corpus, is generally ascribed to a writer of the Cnidian School in the 5th century B.C. Proper allowance being made for the paucity of known anatomical and physiological facts at that time, one will find much to admire in a number of shrewd observations and deductions. E. K.

Psychotherapy of Psychosis. By GUSTAV BYCHOWSKI, M.D., Assistant Clin. Prof. of Psychiatry, New York Univ. College of Med. Pp. 328. New York: Grune & Stratton, Inc., 1952. Price, $5.75.

THE author states that he deems it important to outline a synthesis of our present knowledge in the field of Psychotherapy of Psychoses, in order to have a clear basis on which to build further research and study. At the same time, he wishes to impart through his book some of the spirit of Bleuler and Freud. While there are some case histories, the treatment of the subject is fairly descriptive and theoretical and, hence, designed for a fairly advanced psychiatric clinician. O. E.

NEW EDITIONS

Clinical Practice in Infectious Diseases. By E. H. R. HARRIES, M.D., Lond., F.R.C.P., Formerly Med. Supt., Infectious Diseases Hospitals Service, London County Council, and M. MITMAN, M.D., London, F.R.C.P., Consultant Physician and Med. Supt., River Hospitals. 4th ed. Pp. 717; 20 plates (15 in color) and 48 figs. Baltimore: Williams and Wilkins Co., 1951. Price, $6.50.

THIS book presents the clinical practice in infectious diseases as they are encountered primarily in the British Isles with occasional reference to diseases seen only elsewhere such as tularemia and without mention of certain others such as Rocky Mountain Spotted Fever and the Relapsing Fevers. Within these limitations the book is an excellent one. Its value and popularity are attested by the appearance of a 4th edition only 11 years after the 1st. It is well illustrated with many illustrations in color. The format is convenient. All physicians in general practice will find this a useful text. R. K.

Modern Dietary Treatment. By MARGERY ABRAHAMS and ELSIE M. WIDDOWSON, University of Cambridge. 3d ed. Pp. 355; 18 tables. London: Bailliere, Tindall and Cox, 1951 (Williams & Wilkins, distributor in U. S.). Price, $4.50.

IN concise readable form this textbook gives the dietitian and nutritionist in the United States

a clear picture of dietary practices in England, and provides a ready reference to the oft-quoted British tables of food composition. The contents include a discussion of dietary principles in health and disease, detailed dietary outlines, and recipes.

C. R.

Technical Methods for the Technician. By ANSON LEE BROWN, B.A., M.D. Pp. 784; 304 ills. 4th ed. Columbus, Ohio: Anson L. Brown, Inc., 1951. Price, $10.00.

The Merck Index of Chemicals and Drugs. An Encyclopedia for the Chemist, Pharmacist, Physician, and Allied Professions. 6th ed. Pp. 1,167. Rahway, N. J.: Merck & Co., Inc., 1952. Price $7.50 regular edition, $8.00 thumb-indexed.

THE profession will welcome the appearance of this excellent work which has been thoroughly revised since its last appearance twelve years ago. Its many new features will still further increase its usefulness.

R. K.

Muir's Textbook of Pathology. By D. F. CAPPELL, M. D., F.R.F.P.S.G., Professor of Pathology, University of Glasgow. 6th ed. Pp. 1090; 635 ills. Baltimore: Williams & Wilkins Co., 1951. Price, $10.00.

MUIR'S Pathology has for many years (1st ed., 1924) been a standard British textbook for students of medicine. Professor Cappell, one of Sir Robert's co-workers, has edited a new (the sixth) edition. In comparing the various editions with the last, one is struck with the remarkably little change that has been made and the American pathologist must conclude that British conservatism extends into his medical thinking. The arrangement and content is very similar to the older American texts, the illustrations are adequate but not noteworthy. In brief, the book is still the work of Muir and offers nothing that cannot be found in several standard American texts.

E. A.

Pathological Histology. By ROBERTSON F. OGILVIE, M.D., D. Sc., F.R.C.P. ED., F.R.S.E., Senior Lecturer in Pathology and Assistant in Forensic Medicine, University of Edinburgh. 4th ed. Pp. 494; 295 color ills. Baltimore: Williams & Wilkins, 1951. Price, $8.00.

THE American pathologist who is not familiar with Doctor Ogilvie's text will find here an atlas of microscopic pathologic anatomy with sufficient text devoted to gross pathology and pathogenesis to make it easy reading. It is not intended as a textbook in pathology but rather as a manual for students of microscopy. As such it is the best volume with which this reviewer is acquainted. The photography and reproductions are unusually good, there is a great variety of excellent staining technique and the choice of material is really superb. This volume deserves a wide usage and at its present cost ($8.00), it will probably get it.

E. A.

Metabolic Interrelations. Transactions of the Third Conference, January 8-9, 1951. Edited by EDWARD C. REIFENSTEIN, JR., M.D. Pp. 294; 32 tables, 85 fig. Sponsored by Josiah Macy, Jr. Foundation, New York, N. Y., 1951. Price, $4.00.

THIS third conference on metabolic interrelationships deals again primarily with the biochemistry of bone and skeletal development. Among the 14 papers presented is a series on osteogenesis in which the discussors review results obtained using newer techniques in the study of bone formation and repair. Of particular interest is the work on the osteogenetic potency of transplanted cells. The effect of purified hormones and nutrition upon skeletal morphogenesis in the rat is summarized by the California workers who have long been active in this field. The extensive studies using radiocalcium to determine the metabolic turnover of the skeleton are of interest. This volume should be carefully read by those engaged in metabolic investigation.

C.S.

Endocrine Functions of the Pancreas. By BERNARD ZIMMERMAN, M.D., Department of Surgery, University of Minnesota. Pp. 82; 12 fig. Springfield: Charles C Thomas, 1952. Price, $2.50.

THE initial chapter of this monograph deals with the history of the discovery of insulin and certain methods for producing experimental diabetes. The subsequent chapters include discussions of the chemistry of insulin and its action in animal and human metabolism. An abbreviated account is given of lipid metabolism and the pancreas, while the hyperglycemic factor is reviewed at length. This informative summary of the hormonal functions of the pancreas will be of interest to the clinician.

C.S.

Physicians' Federal Income Tax. By HUGH T. CAMPBELL and JAMES B. LIBERMAN. Pp. 112. Great Neck, New York: Doniger & Raughley, Inc., 1952. Price, $2.50.

Surgery of the Oblique Muscles of the Eye. By WALTER H. FINK, M.D. Pp. 350; 93 ills. including 18 in color. St. Louis: C. V. Mosby, 1951. Price, $8.75.

Doctor's and Dentist's Tax Handbook. By PAUL GITLIN, Member of the New York Bar. Pp. 198. New York: Prentice-Hall, Inc., 1951. Price, $3.70.

The First Annual Report of the National Science Foundation, 1950-51. Pp. 31. Washington, D. C.: U. S. Government Printing Office, 1952. Price, $.20.

Aphorisms of C. H. Mayo and William J. Mayo. By FREDERICK A. WILLIUS, M.D. Pp. 117. Springfield, Illinois: Charles C Thomas, 1952. Price, $2.75.